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THE CLINICAL SIGNIFICANCE OF APICAL AND AORTIC SYSTOLIC HEART MURMURS (WITHOUT DIASTOLIC MURMURS) AS HEARD WITH THE STETHOSCOPE*

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DESPITE the introduction during the last generation of many intricate and useful techniques for the study of the heart and circulation, including electrocardiography with all its newer ramifications, angiocardiography, electrokymography, cardiac catheterization, ballistocardiography, and even phonocardiography itself, the experienced and skillful use of the clinical stethoscope continues to be most helpful. In the hands of at least half of all the doctors in the world it is the only means, along with sphygmomanometry, of supplementing what careful history taking (which by the way still ranks first in diagnosis) and the rest of the physical examination may reveal in any particular patient. It, therefore, behooves us to see that we teach and practice skilled auscultation to the very best of our ability. We are not concerned in the present paper with the vibrations of the heart, that we can record graphically but cannot hear; that is another phase of the subject that is still in its relative infancy in the field of phonocardiography. It is, however, true that some individuals are endowed with a wider range of hearing than others, especially in picking up slight diastolic murmurs, be they aortic or mitral, and some individuals unfortunately grow deaf early. Those problems do always concern us but need no special discussion in connection with the present subject.

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In further introduction we would point out that not infrequently changes in the heart sounds are much more important than the presence or development of murmurs: for example, the appearance of the serious diastolic gallop rhythm (sometimes better felt and seen than heard), indicating ventricular dilatation, the accentuated pulmonary second sound with an overloading of the pulmonary circulation, and the snapping first sound with mitral stenosis.

We wish to assume also, before going further, that the reader is familiar with the grading of the intensity of heart murmurs, to which we have become accustomed in Boston and which we have found very useful and will employ in the rest of this paper. We have divided the intensities into three lots: a) grades 4 and 5 for loud and very loud murmurs, b) grades 2 and 3 for slight and moderate, and c) grades 1 and 0 for very slight or none at all.

Finally, in these introductory paragraphs we wish to emphasize our own preference for the terms *physiological* and *pathological,* as applied to heart murmurs, in the place of the classical *functional* and *organic,* which clinically are misleading. Many so-called functional murmurs have a more serious significance than organic murmurs and, in fact, many heart deaths occur with no murmurs at all. If one wishes to do so, one can divide still further pathological murmurs into those produced by valvular deformity, that is structural or the old "organic," and those that are relative, whether due to dilatation of valve ring or due to dilatation of ventricular cavity. As a matter of fact it is not always possible to distinguish clinically between pathological murmurs that are structural in origin and those that are relative.

SYSTOLIC MURMURS. For generations one of the most difficult problems in auscultation has been to assess the significance of certain systolic murmurs, or indeed of any of them. Diastolic murmurs have always been easier to assess, inasmuch as they are routinely interpreted as pathological and usually readily ascribed to a particular defect. The same is true of continuous murmurs and to some extent of loud and very loud (grades 4 and 5) systolic murmurs. Similarly, it is usually possible to diagnose with satisfactory accuracy the causes of both physiological and pathological murmurs maximal at the pulmonary area, along the left sternal border, and at the end of the sternum. However, systolic murmurs of but slight to moderate (grades 2 and 3) intensity, especially if they are maximal at either cardiac apex or aortic valve area, have been and still are quite often very debatable both as to seriousness and as to mechanism. It is with these murmurs that we are now concerned.

Present data. In 1943, we presented a report on the follow-up study of 187 out of 273 cases with loud and very loud systolic murmurs at the cardiac apex and aortic valve area without diastolic murmurs[1]. These were found among 6,413 cases referred to one of us (P.D.W.) for cardiovascular opinion. It was then planned to make a similar follow-up study of cases with moderate (grade 3) or slight (grade 2) systolic murmurs at the cardiac apex or aortic valve area or both, without diastolic murmurs. This we have now completed and are herewith reporting. For the sake of comparison, tables have been prepared (see Tables 1 and 2) showing the findings in the case of 1) the 1943 study, 2) the present analysis, and 3) a series of 200 consecutive cases with no murmurs at all from the same consulting practice.

Among 7,111 patients 1,777 showed moderate to slight (grade 3 and grade 2) systolic murmurs at the cardiac apex or aortic valve area without diastolic murmurs; 1,212 of these were followed up for the present study. The 200 cases without murmurs were found among 1,000 cardiovascular patients in the same practice.

TABLE 1.—DATA OF CASES WITH SYSTOLIC MURMURS WITHOUT DIASTOLIC MURMURS

Private Cardiovascular Cases	*Series A Grades 4 to 5*	*Series B Grades 2 to 3*	*Series C No Murmurs*
Number of records checked	6,413	7,111	1,000
Number of cases found	273	1,777	200
Number of cases followed	187 (68.5%)	1,212 (68.5%)	
Sex Male	115—60%	751—62%	same
Female	72—40%	461—38%	(3 to 2)
Age Over 50	138	same	same
Under 50	49	(3 to 1)	(3 to 1)
Type of heart disease			
"Degenerative" Coronary		363	44
Hypertensive	124—66.3%	168 = 830 = 68.4%	23 = 80 = 40%
Both		299	13
Rheumatic	50—26.7%	36—3%	0
Syphilitic	1—0.5%		
Congenital	2—1.1%	3—0.3%	
Uncertain or other	10—5.3%	80—6.6%	5—2.5%
None: NCA	0		37
Irritable heart	0	263—21.7%	42 = 115 = 57.5%
Other	0		36
Position of Murmur			
Aortic (maximal)	34—18%	232—19%	
Apical (")	153—82%	668—55%	
Both (equally)		312—26%	

These 3 groups of cases we have compared as to sex, age, presence and type of heart disease, location of murmur, and mortality.

Discussion. PREVALENCE. It is evident in the first place that in a large group of individuals who were referred to a cardiovascular consultant aortic and apical heart murmurs of grades 2 and 3 (of slight to moderate intensity) were much more common, in a ratio of 6½ to 1, than murmurs of grades 4 and 5 (loud to very loud) heard in the same locations, and more common actually by a ratio of about 5 to 4 than cases in the same consulting practice with no murmurs at all.

SEX AND AGE. The sex ratio of 3 males to 2 females was the same for all three groups, and was closely similar to the sex ratio of this consulting practice. Nearly three-fourths of each of the 3 groups were over 50 years old.

TYPE OF HEART DISEASE. There was considerable difference between the 3 groups as to the presence and type of heart disease. Some sort of structural heart disease was present in every case with loud or very loud murmurs but was not found in 22% of the patients who had only slight or moderate murmurs or in 58% of those with no murmurs at all. The exact kind of heart disease remains open to question in a good many of the cases, since this

was a clinical series with infrequent necropsy control. However, so far as we could tell coronary heart disease, hypertensive heart disease, or both were the commonest types in all 3 groups, making up two-thirds of those with loud murmurs, slightly more of those with the lesser murmurs, and 40% of those without murmurs. Coronary heart disease was diagnosed more often than hypertensive heart disease. An uncertain number of these, though certainly a minority, had undoubtedly some rheumatic valvular deformity too. On the other hand, clearcut rheumatic heart disease was evident in 27% of those with loud murmurs, in only 3% of those with the lesser murmurs, and in none of those without murmurs. Congenital heart disease and cardiovascular syphilis were uncommonly found in the murmur groups in contrast to coronary, hypertensive or rheumatic heart disease. This is partly to be explained by the fact that, with respect to congenital defects, children were considerably in the minority in the total series. Furthermore, some instances were doubtless overlooked since some of the cases were seen before the days of current intensive interest in congenital defects, and also due to the fact that with respect to cardiovascular syphilis the patients were all private cases. In retrospect, it is our belief now that "degenerative heart disease" may have been overdiagnosed in the earlier series with grades 4 and 5 murmurs and rheumatic and congenital heart disease underdiagnosed.

POSITION OF THE MURMUR. The murmur was maximally aortic in position in the same relative number of cases in the series with loud murmurs and in that with the lesser murmurs; the ratio was 18% compared with 19%. In 26% of those with the lesser murmurs, there was the same intensity at apex and base, but in those with loud murmurs it was apparently consistently true that the maximum intensity was always at either apex or aortic valve area. It should be noted incidentally that, as we have found before, aortic systolic murmurs are well transmitted to the cardiac apex and poorly to the lung bases while mitral systolic murmurs of the same intensity are well transmitted to the left axilla and lung bases and poorly or not at all to the aortic area.

MORTALITY. The most important aspect of this study concerns the relative mortality in the 3 groups (see Table 2). Within a year of the first examination by the consultant, 44% of those with loud murmurs were dead, while only 28% of those with the lesser murmurs, and 23% of those without murmurs had died. During the second year, another 16% of the original number of cases with loud murmurs died and during the third year another 5%. However, some patients with loud murmurs survived a good many years: 28% for 10 years and 8% for 15 years; these were cases with lesser degrees of cardiac enlargement. Of those with the lesser murmurs 43% survived 10 years and 33% survived 15 years. Of those with no murmurs, 70% were still alive after 10 years and 60% after 15. So far as could be ascertained the death was of cardiac nature in 92% of the loud murmur cases and in 82% of the lesser murmur cases. The male mortality was greater than the female in both groups, mostly by a considerable margin (see Table 2). The so-called "degenerative" cardiac cases, that is, those with coronary or hypertensive heart disease or both, showed a considerably higher mortality than did those with rheumatic heart disease; many of the former were of course older than were the latter. So far as position of the maximal murmur in each group was concerned, there was little to choose

with respect to mortality; certainly the maximal audibility at the aortic site did not prejudice life particularly as has sometimes been thought.

The most important factor of all so far as mortality was concerned was heart size. This is shown best by comparing the 15 year or more survival of those with much enlarged hearts with that of those with no evident enlargement of the heart at the time of our first examination; this held true for both murmur groups, being 97% compared to 68% in the loud murmur cases, and 99% compared to 41% in the lesser murmur cases.

Summary. A follow-up study is herewith reported of a comparison of 1777 cases with slight to moderate (grades 2 and 3) systolic murmurs without diastolic murmurs heard maximally at cardiac apex, aortic valve area or both as compared with 187 patients with loud and very loud (grades 4 and 5)

TABLE 2.—MORTALITY OF CASES WITH SYSTOLIC MURMURS WITHOUT DIASTOLIC MURMURS

	Grades 4 to 5	*Grades 2 to 3*	*None*
Number of Cases	187	1,212	200
Total Mortality			
1 year	44% (48% of "Degenerative" cases)	28%	23%
2 and 3 years	60 and 65% respectively		
10 and 15 years	72 and 92% respectively	57 and 67% respectively	30 and 40% respectively
Cardiovascular Deaths	92%	82%	
Sex Mortality—M:F	*Total Males: Total Females*		
10 years	78%:92%	63%:46%	
15 years	63%:92%	73%:57%	
Type of Heart Disease Mortality			
"Degenerative" Coronary 10 years	Total degenerative 10 years =85%	90% Total degenerative 15 years =91%	80% Total degenerative 10 years =78%
"Degenerative" Coronary 15 years			91%
"Degenerative" Hypertensive 10 years		88%	63% Total degenerative 15 years =95%
"Degenerative" Hypertensive 15 years	Total degenerative 15 years =98%		
"Degenerative" Cor. and Hyp. 10 years			92%
"Degenerative" Cor. and Hyp. 15 years		95%	100%
Rheumatic 10 years	47.5%		
Rheumatic 15 years	75.7%	22%	
Uncertain or miscellaneous 10 years	50%		
Uncertain or miscellaneous 15 years	80%		
None: NCA, etc.			Rare deaths
Position of Murmur in Relation to Mortality			
Aortic 10 years	65%	51%	
Aortic 15 years	96%	64%	
Apical 10 years	74%	58%	
Apical 15 years	92%	67%	
Both sites 10 years		58%	
Both sites 15 years		70%	
Heart Size			
15 year mortality: Much enlarged	97%	99%	
15 year mortality: Moderately enlarged	94%	93%	
15 year mortality: Slightly enlarged	82%	78%	
15 year mortality: Not enlarged	68%	41%	

systolic murmurs without diastolic murmurs heard in the same locations and with 200 patients with no murmurs at all. All 3 groups were encountered in a private cardiac consulting practice.

Patients with grades 2 and 3 murmurs were slightly more frequent than those without murmurs and much more common by a ratio of 6½ to 1, than those with grades 4 and 5 murmurs. The ratio of males to females (3 to 2) and the age incidence (majority over 50 years old) were the same for all 3 groups.

Patients with coronary or hypertensive heart disease, or both, outnumbered other kinds of heart disease in all three groups but so far as this clinical study allowed, there seemed to be a great difference in the prevalence of rheumatic heart disease, being found clearly in 27% of those with loud murmurs, in only 3% of those with lesser murmurs and in none of those without murmurs. There was a minority of cases with other or uncertain kinds of heart disease.

The site of the maximal systolic murmur was aortic in contrast to apical in about one-fifth of the patients with either loud or lesser murmurs but in the case of the latter there seemed to be little difference between the aortic and apical intensities in 26%.

The most important aspect of this follow-up study concerns mortality. The 4 most interesting and important findings were the following:

1) Those with the loudest murmurs lived shorter lives than those with lesser murmurs or with no murmurs at all, but there were occasional cases (actually 8%) with grades 4 and 5 murmurs who were still alive more than 15 years after the murmurs were recorded by us as loud or very loud. The intensity of the murmurs, however, as a factor in influencing mortality was qualified by three other important findings.

2) The male mortality was greater than the female in all the groups.

3) A background of coronary or hypertensive heart disease was much more serious than that of rheumatic heart disease; a younger age here doubtless favored some of the rheumatic cases.

4) This study revealed no evidence that aortic systolic murmurs of slight, moderate, loud, or very loud intensity, but without diastolic murmurs, have any more unfavorable prognosis *per se* than the corresponding apical systolic murmurs.

5) One of the most impressive findings of all was that moderate to much enlargement of the heart greatly favored an earlier ending of life in all the cases. This was a more important factor in all the series than any other, including loudness of the murmur itself, for heart size is a better indication than are murmurs of the degree of strain on the heart. Many murmurs show the presence of strain-producing valvular defects but such defects vary greatly in importance, as do patients in their ability to resist such strain.

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THE NATURE OF CIRCULATORY FAILURE IN ACCIDENTAL DEATH*

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It has been shown that during the process of death the first physiological process to fail varies in different types of accidental death: sometimes the breathing fails first; sometimes an irreversible insult to the brain, caused by anoxia, is done first; and sometimes the circulation fails first[14]. It is the purpose of this study to examine closely the nature of the circulatory failures and also of the circulatory recovery by resuscitation.† The failure is known to be abrupt: the circulation collapses over a period of about a minute, with the blood pressure falling from 150/70 to 30/10 during this short time[14]. Two explanations for the failure have been offered: one that it is due to myocardial failure and the other that it is due to peripheral vasomotor collapse[14,17]. The latter would be caused by the strong anoxia and acidosis which is characteristic of the process of death[13], which in turn would induce a widespread systemic vasodilation[7] and consequently a decrease in peripheral resistance and blood pressure. This viewpoint has been well described by Moon[8]. At postmortem examination, interstitial bleeding, capillary congestion and edema are frequently found, these being the pathological concomitants to the assumed vasomotor collapse. Moon was particularly concerned with the slow circulatory failures of traumatic shock; these, of course, take hours. In the more rapid anoxic deaths, however, he suggests that there may not be time for the vasomotor change to occur.

The alternative theory that myocardial failure, and not peripheral vascular failure, is primarily involved is supported by the work of Sands and DeGraff[9]. They found a decrease in cardiac contractility as extreme anoxia supervened. We have also argued that because cardiac massage, administered just after collapse, induces blood pressures to about 110/30, the peripheral vascular bed must be in fair condition and hence the collapse is presumably myocardial[14]. Another piece of evidence favoring the myocardial failure hypothesis is to be found in the electrocardiograms during recovery: the elevated T wave, which is characteristic of anoxia, abruptly re-

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† In the accidental deaths entailing ventricular fibrillation, primarily electric shock and fresh water drowning, the circulatory collapse is of course myocardial. However, in this report only the non-fibrillatory collapses will be considered.

verses during the first few heart beats of recovery[11]. Hence, a change in the myocardium and not the periphery may be presumed responsible for recovery. It may, therefore, be deduced that the original failure must have been primarily myocardial in nature.

In the present experiment the nature of the failure was investigated in another way. Advantage was taken of the anatomical position of the myocardium in the circulatory path. The organ is supplied with blood from the aortic sinuses, whereas peripheral organs like muscle or gut or skin, where the postulated vasodilation would take place, are more distant from the left heart. Therefore, the blood which is reoxygenated during resuscitation must reach the myocardium first. Two questions were posed. First, where, very early in recovery, will reoxygenated blood be found: in the heart alone or in the heart and periphery as well? If the former, then presumably myocardial failure was originally involved; if the latter, then peripheral failure as well was involved. Second, if one attempts to resuscitate just beyond the point of circulatory failure, at the point where we know that the attempt just fails, will reoxygenated blood be found in the heart and not the periphery? If so, then recovery must entail reoxygenation of the periphery and, therefore, the original failure must have involved the periphery.

Methods. Unanesthetized dogs were given pure nitrogen to breathe as described previously[14]. When unconscious from anoxia, the femoral artery was exposed and cannulated for recording blood pressure. The recording apparatus was so arranged that the blood pressure fluctuations could be continuously observed, as well as continuously recorded. When the systolic blood pressure fell to 80 to 90 mm. Hg, the trachea was quickly cannulated and the lungs periodically inflated and deflated with a respiratory pump.* This point during the process of death has been shown to be the threshold of death for resuscitation by this technique, because if one waits some 12 seconds longer, when the systolic blood pressure falls to 60 mm., the attempted resuscitation always fails[15]. In dogs resuscitated just at the threshold of death, the blood pressure continues to fall for about 15 seconds more and then suddenly starts to rise, mounting rapidly in the course of some 30 cardiac contractions to about 150/30[11]. It was just before this point that we wished to ascertain the location of reoxygenated blood in the vascular system. Circulation was, therefore, arrested just after the blood pressure had commenced its abrupt climb: ventricular fibrillation was induced by passing 110 volt, 60-cycle, AC current through needle electrodes, inserted subcutaneously on either side of the chest. Figure 1 illustrates one such experiment.

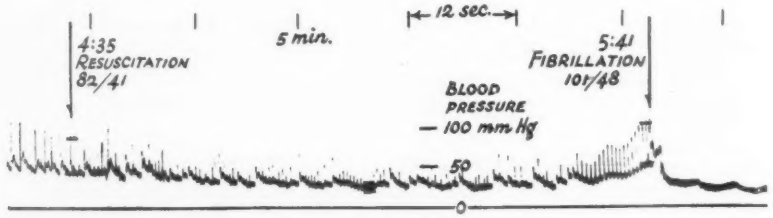

FIG. 1.—Ventricular fibrillation just after start of recovery of blood pressure.

The chest was then opened and a hemostat was clamped tightly on the root of the aorta. Care was exercised to avoid "milking" ventricular blood into the aorta. Then 5 cc. blood samples were drawn from the left

* The Emerson "Resuscitator", furnished by the courtesy of the J. H. Emerson Co., Cambridge, Massachusetts.

ventricle, the ascending aorta just above the hemostat, and the abdominal aorta at the level of the renal arteries. The samples were then analyzed for oxygen, in duplicate, by the manometric method of Van Slyke and Neill[16]. The hemoglobin content was also analyzed photocolorimetrically. To determine the per cent oxygen saturation, the ratio of observed oxygen content to the hemoglobin content was computed and then multiplied by 100/1.35.

Exactly the same procedure was followed in another group of dogs, except that the resuscitating maneuver was started when the systolic pressure had fallen to 56 to 60 mm. Hg. As discussed above, resuscitation just fails at this point in the process of death. It takes about 12 seconds for the systolic blood pressure to decline from 80 mm. Hg to 60 mm. Hg. The second group of dogs, therefore, was subjected to the resuscitating maneuver 12 seconds later in the process of death than the first group. In the first group, the attempted resuscitation uniformly succeeded; in the second, it uniformly failed. No ventricular fibrillation was used in the second group, for circulation was never restored.

TABLE 1.—OXYGEN CONTENT OF BLOOD FROM VASCULAR TREE

	Start resuscitation at:		*Fibrillation at:*			*% O_2 saturation of blood from*		
Dog Number	*Blood pressure*	*Time*	*Blood pressure*	*Time*	*Hemoglobin, gm./100 cc.*	*Left Ventricle*	*Ascending Aorta*	*Abdominal Aorta*
1	86/57	5:37	85/57	5:59	14.9	74	59	11
2	90/40	4:18	75/31	4:46	9.3	100	69	2
3	82/40	2:46	131/27	3:04	10.9	78	70	13
4	88/47	2:32	116/43	3:07	12.3	83	62	11
5	82/51	3:15	98/52	3:35	15.1	70	38	12
6	82/41	4:35	101/48	5:41	9.2	85	58	21
Means	85/46		101/43			82	59	12
7	60/41	4:32	No fibrillation		8.5	79	27	3
8	58/40	4:32	"	"	14.4	54	10	1
9	58/28	5:26	"	"	15.4	37	11	2
10	56/30	4:03	"	"	10.2	74	29	6
Means	58/35					61	19	3

Results and Discussion. The data for 6 dogs which were resuscitated and 4 dogs in which the attempt to resuscitate just failed are shown in Table 1. In the successes, abdominal aortic blood was 12% saturated with oxygen, while in the failures, the blood was 3% saturated. One can assume that blood from this locus gives a good sample of major arterial blood throughout the vascular tree. Hence, the very low saturations of the blood make it apparent that reoxygenated blood never did reach the arterioles of the peripheral vascular system in any quantity in either group of experiments. But in the first experiment, the successful resuscitations, blood from the ascending aorta was 59% saturated with oxygen. Obviously some of it must have flowed into the coronaries and must have caused the observed recovery of contractility and blood pressure. In the unsuccessful resuscitations, the saturation of the blood from this same locus was 19%. Although this saturation is adequate to resuscitate at higher blood pressures[2], evidently at these low blood pressures not enough time elapsed before cardiac standstill for blood to be circulated through the coronaries. Hence no recovery took place.

It is concluded that the failure of blood pressure and circulation in this

type of accidental death is myocardial in nature. The peripheral vascular bed is not involved. We have studied circulatory failure in several other types of accidental death: acute anoxia (breathing 2.43% O_2), carbon monoxide poisoning, obstructive asphyxia and sea water drowning, and in all of them the circulatory failure is the same in its over-all aspects: it collapses suddenly, the electrocardiographic changes are similar, and it is restorable at the same rates and with the same maneuvers[11,12,13,14,15]. We, therefore, conclude that the circulatory failures in all of these different types of death are in all probability similar in nature. They are all failures of cardiac contractility due to anoxia.

Birnbaum and Thompson reported that dogs can be resuscitated by insufflating their lungs with "pure nitrogen" gas[1]. We have failed entirely to confirm this experiment[2]. Furthermore, we have suggested that the results reported by Birnbaum and Thompson were due to the use of nitrogen contaminated with oxygen, since 2% oxygen in nitrogen is entirely efficacious in resuscitating and since commercial nitrogen is often contaminated with 2 or even 3% oxygen[2,12]. The present experiment also shows that the conclusions of Birnbaum and Thompson are faulty, for the real nature of circulatory recovery has herein been shown to be reoxygenation of the myocardium.

Gordon and Turner[5] have recently reviewed the pathological changes to be observed at postmortem examination of men dying from rapidly supervening anoxia. After examining critically the matter of interstitial bleeding, petechial hemorrhages, and so forth, that are so often observed in these cases, they stress the nonspecific character of such changes and emphasize that they must not be accepted as pathognomonic of asphyxial death. The present study furnishes additional information about the matter. These dogs were dying in an overwhelming anoxia and acidosis. One might therefore expect, as already discussed, considerable vasodilation; one might also expect increased capillary permeability and increased capillary leakage. But we doubt, because of the experimental evidence, that any of these occurred early during the death process: in the first place, the circulatory collapse, both from the data of Sands and DeGraff and from the data reported here, is definitely myocardial. In the second place, the state of the vascular bed is governed not only by metabolites but also by the vasomotor centers of the nervous system. In severe anoxia, as in many other emergencies, the central nervous impulses undoubtedly predominate, so that there is a strong vasoconstriction, with reduced blood flow in skin, muscles and abdominal viscera[3,4,6]. This, of course, is part of the response of the whole body to extreme emergencies, to which Cannon has called attention. It is, in all probability, only after circulation has failed for a long time and hence the vasomotor function of the brain has ceased, that the dilation and permeability change, so often apparent at necropsy, takes place. During the actual process of circulatory failure, it is not present. This conclusion is true for accidental and rapidly occurring deaths. It also probably applies, considering especially the data of Stead and Warren[10], to skeletal muscle and skin in the relatively slow deaths from traumatic shock, heart failure, and so forth, that are usually observed in hospitals. But in the latter type of lingering failure, it is thought that visceral, and particularly splanchnic visceral, vasodilation along with the permeability change, probably occurs.

Summary. Dogs were resuscitated when on the threshold of circulatory

failure. Then just as circulatory recovery had commenced, the sites of reoxygenation of blood in the vascular tree were ascertained. It was found that reoxygenated blood had reached the left heart and ascending aorta but had not yet reached the abdominal aorta in any quantity. It is therefore apparent that circulatory recovery entails reoxygenation of a myocardium failing from anoxia, rather than reoxygenation of the peripheral vascular tree, presumed to have undergone vasomotor collapse. The aim of resuscitating measures, therefore, given the condition of near-death due to circulatory failure, is reoxygenation of the myocardium.

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SODIUM SALICYLATE IN RHEUMATIC FEVER; EFFECT OF ADJUVANT MEDICATION

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THE salicylates continue to play an important role in the management of rheumatic fever despite the beneficial effect observed with ACTH and cortisone. Prior to the advent of the latter drugs, Coburn[4] had reported apparent alteration of the rheumatic process with doses of salicylate sufficient to maintain blood levels above 35 mg. per 100 cc. In light of this, it was of some concern that sodium bicarbonate, often administered for the accompanying gastric distress, was found to cause a marked lowering of the salicylate level[18]. Although Coburn's critical level assumes less importance since several investigators have questioned the specific anti-rheumatic action of the salicylates[8,13,20], it seemed worthwhile to study the effect that various antacids might exert.

Method. The investigation was conducted in an Army hospital on rheumatic fever patients ranging in age from 18 to 38 years. The diagnosis was based on criteria outlined by Jones[12]. In addition to various joint and cardiac manifestations, all subjects had elevated erythrocyte sedimentation rates, prolonged P-R intervals or both. The patients were maintained on a regular schedule of 1.6 gm. of enteric coated sodium salicylate every 4 hours, a total of 10 gm. a day, together with the particular adjuvant drug being studied. The enteric form was used since the staff had previously been impressed by the fact that patients tolerated it better than the uncoated sodium salicylate or aspirin. Adjuvants studied included sodium bicarbonate, magnesium trisilicate*, aluminum hydroxide gel and aluminum hydroxide tablets. Medication was given on a 6 - 10 - 2 - 6 - 10 - 2 schedule and blood samples for salicylate determinations were drawn at 8 a.m. every second day. Each combination of medication was given for 8 to 12 days, which allowed a minimum of 4 salicylate determinations in each case. Many patients participated for several weeks, taking each of the combinations in succession.

Salicylate tests were made on plasma after the technique described by Brodie, Udenfriend and Coburn[2]. Carbon dioxide combining power determinations were made according to the method of Van Slyke and Cullen.

Results. The average of the 4 or more salicylate determinations for each individual receiving a particular combination of drugs was calculated. Table 1 shows the ranges of these values, and the average for each group.

Enteric coated sodium salicylate given alone resulted in an average plasma level of 42.2 mg. per 100 cc. for 24 cases. The averages for the patients with the lowest and highest concentrations were 33.4 and 57.0 respectively. The majority of the patients tolerated the medication with no more than moderate gastric disturbances but a few were severely upset. Apprehension and irritability accompanied the higher concentrations.

Sixteen patients received 1.6 gm. of sodium bicarbonate in 0.32 gm. tablets with their salicylate every 4 hours. This resulted in an average plasma level of 29.8 mg. with a minimum of 24.9 and a maximum of 37.0. Practically no one experienced nausea, but several complained of bloating and gaseous eructations.

* Courtesy Eli Lilly Company.

A total of 17 patients received 0.65 gm. of sodium bicarbonate with each dose of salicylate. On this combination the lowest average concentration for any patient was 26.7 mg. per 100 cc., the highest 48.6. The average for the entire group was 35.9. Few gastric complaints arose, and the patients in this group were, on the whole the most comfortable of any participating in the investigation.

Thirteen patients receiving 1.0 gm. of magnesium trisilicate (2 tablets) with each dose of salicylate demonstrated levels ranging from 38.8 to 54.2, with an average of 43.0 mg. per 100 cc. Some of those achieving the higher concentrations suffered dyspnea, nervousness and anorexia, but rarely gastric distress.

Nine patients received aluminum hydroxide in tablet form, averaging 46.5 mg. per 100 cc. with a range of 40.0 to 54.0. Gastric discomfort was minimal but the typical symptoms of nervous irritability accompanying high salicylate levels were prominent.

Sixteen patients were started on 8 to 16 cc. of aluminum hydroxide gel with each dose of salicylate, but 5 soon became so nauseated they could not continue to take their medication. They objected mainly to the bulkiness of the drug, which precipitated vomiting as they swallowed it. The average salicylate level for the 11 patients who continued on the program was 49.8 mg. per 100 cc., the lowest and highest being 42.8 and 59.2 respectively.

Carbon dioxide combining power determinations were made on a representative number of patients receiving each combination of drugs, as shown in Table 2. The average salicylate levels for the patients on whom this test was performed are also shown.

It is immediately apparent that the higher salicylate levels were accompanied by depression of the CO_2 combining power. This situation was not affected by administration of the nonabsorbable antacids, but adequate doses of sodium bicarbonate restored the CO_2 combining power to normal, at the same time depressing the salicylate level.

Incidental observations were the apparent lack of effect of salicylate administration on elevated erythrocyte sedimentation rates and prolonged P-R

TABLE 1.—PLASMA SALICYLATE LEVELS RESULTING FROM ADMINISTRATION OF 1.6 GM. OF ENTERIC COATED SODIUM SALICYLATE EVERY 4 HOURS, ALONE, AND WITH VARIOUS ADJUVANTS

Drug Combination	*Cases*	*Plasma Salicylate Level in mg. per 100 cc.*	
		Range	*Average*
Sodium salicylate alone	24	33.4–57.0	42.2
Salicylate with 1.6 gm. sodium bicarbonate	16	24.9–37.0	29.8
Salicylate with 0.65 gm. sodium bicarbonate	17	26.7–48.6	35.9
Salicylate with magnesium trisilicate	13	38.8–54.2	43.0
Salicylate with aluminum hydroxide tablets	9	40.0–54.0	46.5
Salicylate with aluminum hydroxide gel	11	42.8–59.2	49.8

intervals, and the absence of any hemorrhagic manifestations.

Discussion. The depressing effect of sodium bicarbonate on the salicylate level of the plasma has been adequately explained by Smith *et al.*[17] and confirmed by Hoffman and Nobe[10]. They found that as the pH of the urine was raised by administration of sodium bicarbonate, salicylate excretion increased. On the basis of this explanation, it is easy to see why the non-absorbable antacids cause no such effect. Indeed, if the high levels found with the latter are confirmed by further studies, it might be postulated that their acid-adsorbing properties are in some way interfering with the usual mechanism of salicylate excretion.

Diminished CO_2 combining power may represent respiratory alkalosis or metabolic acidosis, the end result being the same if fully compensated[6]. Clinically, however, compensation is seldom complete and study of the blood pH reveals which process is taking place. No pH studies were made in this investigation, but Bowen, Ronfa and Clinger[1] in their salicylate study found the pH elevated. This likely represents respiratory alkalosis induced by hyperventilation resulting from central nervous system irritation. Sodium is excreted in an attempt to restore the $H{\cdot}HCO_3{:}B{\cdot}HCO_3$ ratio [7,14,16]. Ketosis may develop secondarily and further deplete the alkali reserve[9]. The tendency for sodium bicarbonate to correct the CO_2 combining power deficit probably depends on two or more factors. It lowers the salicylate level, thus favoring more normal breathing; and it offers a supply of sodium to restore the depleted base. The non-absorbable antacids bring neither of these factors into play.

TABLE 2.—EFFECT ON CO_2 COMBINING POWER OF ADMINISTRATION OF 1.6 GM. OF ENTERIC COATED SODIUM SALICYLATE EVERY 4 HOURS, ALONE, AND WITH VARIOUS ADJUVANTS

Drug Combination	*Cases*	*Average Plasma Salicylate Level, mg. per 100 cc.*	*CO_2 Combining Power Volumes Per Cent*
No medication	3	—	56
Sodium salicylate alone	6	40	40
Salicylate with 1.6 gm. sodium bicarbonate	3	31.2	56
Salicylate with 0.65 gm. sodium bicarbonate	3	36.1	44
Salicylate with magnesium trisilicate	4	45.4	42
Salicylate with aluminum hydroxide tablets	2	46.4	42
Salicylate with aluminum hydroxide gel	4	49.1	40

Although the diminished alkali reserve apparently had no harmful effects, the experience in one case demonstrated the narrow margin of safety which exists when the higher salicylate levels are reached. This patient had been maintained at a 50 mg. level for several days when he was given 1.0 gm. of ammonium chloride. Within a few hours he became comatose and the CO_2 combining power was found to be 18 volumes per cent. Unfortunately no CO_2 determination had been made prior to the episode. Recovery was rapid following administration of M/6 sodium lactate.

The depression of the erythrocyte sedimentation rate with large doses of salicylates observed by some workers [4,14], and interpreted as evidence of suppression of the rheumatic process, has been suggested by others[11,15] to be a non-specific effect, possibly mediated by toxic action on the liver. However, Butt *et al.*[3] demonstrated that therapeutic doses of salicylates caused no significant abnormality in the usual liver function tests. In their study of hypoprothrombinemia they encountered no serious hemorrhagic manifestations. Coombs, Higley and Warren[5] observed no severe hypoprothrombinemia until the plasma salicylate level reached 60 mg. per 100 cc.

Although serious complications rarely result from administration of 10 gm. of sodium salicylate daily, a significant percentage of the patients are quite uncomfortable on this dosage. Until better evidence is presented and confirmed by subsequent investigators that salicylates favorably alter the rheumatic process, such a heavy dosage seems unjustified, particularly since the advent of ACTH and cortisone.

Most patients will tolerate the somewhat smaller doses of enteric coated sodium salicylate sufficient to relieve rheumatic discomfort without any adjuvant medication. For those complaining of gastric distress magnesium trisilicate, aluminum hydroxide in tablet form or sodium bicarbonate in 0.65 gm. doses will give satisfactory relief. Impending heart failure, of course, should preclude the use of sodium bicarbonate.

Summary and Conclusions. Sodium salicylate in massive doses lowers the CO_2 combining power.

Sodium bicarbonate depresses the plasma salicylate level and tends to return the diminished CO_2 combining power to normal.

Magnesium trisilicate and aluminum hydroxide gel tablets are as effective as sodium bicarbonate in relieving gastric distress due to salicylate administration but do not lower the plasma salicylate level or raise the CO_2 combining power.

Massive doses of salicylate seldom result in any harmful effect, but cause considerable discomfort.

With the availability of ACTH and cortisone, it does not seem justifiable to give more salicylate than the amount necessary to relieve rheumatic discomfort, until there is more proof that salicylates actually alter the rheumatic process.

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THE ASSOCIATION OF POLYCYSTIC KIDNEYS WITH INTRACRANIAL ANEURYSMS AND OTHER RELATED DISORDERS

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POLYCYSTIC disease of the kidneys and so-called "berry" aneurysms of the intracranial arteries are generally considered to be the result of congenital developmental defects. The presence of both these lesions in one individual may, therefore, represent a relationship that is more than coincidental. For this reason an analysis and evaluation of previously reported cases of the simultaneous occurrence of these two types of lesions and the reporting of 3 additional cases from this laboratory seems timely.

It is well known that congenital polycystic renal disease is often found in association with other developmental anomalies, some of which are trivial and of little practical importance, while others are so disabling as to be incompatible with life. It is also recognized that polycystic renal disease is of grave clinical significance at two particular age periods, namely, during the neonatal period up to one year of age, and in adult life in the neighborhood of 40 years and beyond. While it is the consensus of most workers that the pathologic changes in the polycystic kidneys are the same in these two clinical groups, Lambert[36] believes that the cysts in infants are virtually all blind and functionless, while many of the cysts in adult kidneys are functional and directly communicate with excretory tubules and the renal pelvis.

A distinctive group of anomalies often accompanies congenital cystic renal disease in each of these age periods. Thus in the younger group there may be present such defects of the central nervous system as anencephaly, meningocele and spina bifida; anomalies of the genitourinary system including absence of one kidney, aplasia of calyces or pelves, hydroureter, hypospadias, occlusion of urethra, double vagina and undescended testis; disorders of the gastrointestinal tract such as absence of anus, atresia of rectum, absence of gallbladder and hare lip; and finally, abnormalities of the extremities, like polydactylism and club foot[4,21,49,60,72]. In the older age group aberrant biliary cysts of the liver and cysts of the pancreas are anomalies frequently observed in association with polycystic renal disease. Furthermore, Norris and Tyson[52,53] have concluded that the cystic changes in these 3 organs result from a similar type of defective embryological development[51].

While some intracranial "berry" aneurysms, more particularly in older subjects, may be due to arteriosclerosis, most of these aneurysms, especially those in the Circle of Willis and its major branches, are now generally conceded to be due to some developmental defect of the arterial wall, the exact nature of which is unsettled. Although it is doubtful that the aneurysmal sac itself is actually present in early life, the defect in the arterial wall most certainly is. This zone of weakness, usually located at or near the point where a branch originates from the artery or

the artery bifurcates, dilates or gives way as a result of several factors including intravascular pressure, the unique strains and stresses imposed upon intracerebral vessels and sometimes even arteriosclerosis. The aneurysmal sac is the result.

In the literature on congenital intracranial aneurysms the possibility of other associated developmental defects has only infrequently been considered. However,[4] coarctation of the aorta, a relatively uncommon congenital disorder, has been found in association with intracranial aneurysms often enough for the potential relationship of these two lesions to be well recognized[80]. In similar fashion there have appeared some reports and casual references to the association of intracranial aneurysms and polycystic kidneys. Suspected coexistence of these two disorders on the basis of clinical findings has been reported only 3 times, and in most instances, the aneurysms or the polycystic kidneys, or both, have been incidental necropsy findings.

In the following 3 cases, necropsy disclosed the clinically unsuspected association of intracranial aneurysms and polycystic disease of the kidneys. In the first case, death was due primarily to the leaking or slow bleeding from an intracranial aneurysm and the presence of polycystic kidneys had not been recognized clinically. In the second case, death was due to uremia from failure of the polycystic kidneys and the presence of a symptomless intracranial aneurysm was disclosed by careful examination of the cerebral arteries. In the third case, the illness and death of the individual were due to widespread bronchogenic carcinoma and the presence of two minute unruptured intracranial aneurysms and of polycystic kidneys were accidental post-mortem discoveries.

Case Reports. CASE 1. Leaking congenital aneurysm of left internal carotid artery with death one week after surgical ligature. Bilateral congenital polycystic kidneys.

E. G., a 33-year-old white man, first experienced left frontal headaches 2 weeks before admission. Drooping of the left eyelid, diplopia, and sporadic projectile vomiting developed a few days later. One week before admission he was found unconscious and incontinent and remained semicomatose until hospitalization.

Clinical examination and carotid angiograms revealed abnormal vascular changes consistent with an intracranial aneurysm of the superior portion of the left internal carotid artery. Therefore the left internal and external carotid arteries were ligated in the neck. Subsequently craniotomy was performed and an aneurysm of the left internal carotid artery was isolated by means of a silver clip placed immediately below the left posterior communicating artery. No clinical improvement followed this procedure and the patient died one week later.

Necropsy, performed 9 hours after death, revealed no significant gross abnormalities of the abdominal and thoracic viscera, with the exception of the kidneys, which were diffusely cystic and greatly enlarged, weighing 540 gm. each. The smooth-lined cysts, which ranged in size from 0.5 to 2 cm. in diameter, were present throughout the parenchyma of each organ. The watery fluid in the cysts was clear or turbid and ranged in color from yellowish-brown to dark purple. In essence these symmetrically enlarged kidneys exhibited almost complete replacement of normal renal parenchyma by great numbers of various sized cystic structures, a characteristic gross feature of congenital polycystic kidneys. Microscopically the renal architecture was distorted and virtually replaced by great numbers of small and large cysts lined by flattened epithelium resting on a thin layer of vascular fibrous tissue. The residual uninvolved renal parenchyma was congested.

The surgically removed cranial bone flap was in good apposition. The brain was swollen, congested, and weighed 1580 gm. A small "berry" aneurysm of congenital type, measuring 0.3 cm. in greatest dimension, was present on the left internal carotid artery just below the point where the posterior communicating artery took origin. A silver clip occluded the carotid artery just distal to the aneurysm and beneath the communicating branch. A small amount of partly clotted blood was present on the surface of the aneurysmal sac and there was diffuse sub-

arachnoid hemorrhage adjacent to the aneurysm.

CASE 2. Unruptured congenital aneurysm of secondary branch of right middle cerebral artery. Bilateral congenital polycystic kidneys. Biliary cysts of liver. Cysts of pancreas. Death from renal failure.

J. H., a 62-year-old white man, had been in coma as a result of severe renal failure for 24 hours when brought to the Albany Hospital. He died a few minutes after admission.

A necropsy, performed 15 hours after death, revealed the presence of bilateral enlarged polycystic kidneys, the right weighing 840 gm. and the left 740 gm. The entire parenchyma of both organs was distorted by multiple cysts which measured from 1 to 3.5 cm. in diameter, and presented a variety of colors, ranging from yellow, blue-gray and green to dark red. On gross examination normal renal parenchyma could not be identified and little recognizable functioning tissue was found on microscopic study either. What remained of the renal tissues consisted of little more than dense connective tissue in which portions of distorted nephrons were present, separated by cystic spaces lined by cuboidal or flat epithelium.

The arteries at the base of the brain were somewhat tortuous and showed small focal atheromata. A small unruptured but typical "berry" aneurysm of congenital type, measuring 0.2 cm. in diameter, was present at the junction of a secondary branch of the right middle cerebral artery.

The liver, which weighed 1680 gm. and was of normal size, contained numbers of cystic spaces distributed irregularly throughout the parenchyma. These measured up to 1.5 cm. in diameter. They were located in the region of the portal triads and were lined by flattened or cuboidal epithelium that had some of the characteristics of bile duct epithelium.

While no cysts were observed on gross examination of the pancreas, histologic sections revealed numerous small dilated ducts lined by cuboidal epithelium, obviously, minute cystic structures.

Death of the patient was undoubtedly due to renal insufficiency resulting from polycystic disease of kidneys.

CASE 3. Unruptured congenital aneurysms of the Circle of Willis. Bilateral congenital polycystic kidneys. Death due to bronchogenic carcinoma with widespread extension and metastases.

A. G., a 52-year-old white man, had noted the appearance of a mass in the neck below the left mastoid process in early 1950. A biopsy elsewhere at that time revealed the presence of a malignant tumor which was then treated by Roentgen irradiation. He was admitted to the Albany Hospital during September, 1951, because of increasing pain and disability associated with enlargement of the mass in the neck. On the eighth hospital day, sudden massive bleeding from his mouth occurred and he died within a few minutes. Death was presumably due to hemorrhage from erosion by the carcinoma of a major vessel in the neck.

Necropsy, performed 13 hours after death, disclosed clinically unsuspected bilateral polycystic kidneys. The right kidney weighed 800 gm. and the left 620 gm. On section both organs showed generalized cystic changes with only moderate amounts of functioning renal parenchyma interspersed between the cysts, which ranged from 1 to 5 cm. in diameter.

Two minute unruptured "berry" aneurysms were also found on examination of the cerebral arteries. One of these, which measured 0.3 by 0.2 by 0.2 cm. in size, was present at the junction of the right anterior cerebral artery and the anterior communicating artery; the other was located at the junction of the anterior and middle cerebral arteries at the termination of the right internal carotid artery. It measured 0.2 by 0.1 by 0.1 cm.

The liver weighed 1840 gm. and contained numbers of biliary cysts which ranged from 1 to 6 cm. in diameter. Cystic lesions were not found in any other organ.

Actually, the major pathological process which was responsible for this man's death was bronchogenic carcinoma of small-cell or anaplastic type which apparently arose on the right and was widely disseminated throughout the mediastinum, left lung, and the structures of the left side of the neck.

REVIEW OF PREVIOUSLY REPORTED CASES. In 1904, Dunger[23] discussed the association of polycystic disease and intracranial aneurysms, cited 4 instances[9,69], and reported the death from a ruptured aneurysm of a 54-year-old woman whose daughter had died at the age of 26 from a pontine hemorrhage which may have been due to an aneurysm. Casual references or detailed single case reports give 7 more instances[25,26,33,41,48,75,79]. Two cases are recorded by Suter[73], 2 by Sahs and Keil[65], 3 by O'Crowley and Martland[55], 5 by Ask-Upmark and Ingvar[1] and 7 by

Brown[11]. One of the 3 cases reported by Snapper and Formijne[71], one of the 2 cases of Madonick *et al.*[44], and 6 of the 7 cases reported by Brown[11] seem valid.

From a clinical standpoint Case 1 of Snapper and Formijne[71], Case 2 of Madonick, Savitsky and Hochfeld[44], and Case 1 of Brown are most interesting, since the suspected coexistence of intracranial aneurysm and polycystic disease was an ante-mortem impression. However, the presence of subarachnoid hemorrhage, the only factor established clinically in these cases, does not of itself ensure the presence of an anuerysm without verification by at least one of 3 procedures, namely, arteriography, surgery, or necropsy; although conversely, the clinical methods for establishing the diagnosis of polycystic kidneys made in these 3 cases need not be questioned. Since Case 3 of Snapper and Formijne, Case 1 of Savitsky *et al.*, and the other 6 cases of Brown had the presence of an intracranial aneurysm and polycystic kidneys verified at necropsy, they are fully acceptable. Case 2 of Snapper and Formijne should be excluded from consideration since an intracranial aneurysm was found in association with but a large solitary cyst of one kidney and not polycystic kidneys of congenital type. Thus 32 acceptable cases, not including the 3 probable cases diagnosed clinically, have been reported.

Critical evaluation of many cited cases is not possible since many authors make only a passing reference linking polycystic renal disease with intracranial aneurysms. Yet paucity of detailed pertinent information does not of itself seem sufficient reason to invalidate any of the cited instances. For polycystic renal disease and intracranial aneurysms are entities readily recognized, needing little confirmatory proof of competent observation. Only those reports where the observer himself presents manifestly unsound data need be questioned. Much of the available pertinent correlative information on these two disorders has been well systematized and tabulated by Suter[73].

An equivocal example was noted by Magee[45]. He observed that of 58 persons who came to necropsy following spontaneous subarachnoid hemorrhage, a ruptured aneurysm was the demonstrable cause of hemorrhage in 43 instances. In his report he casually mentions that cystic kidneys were present in one of these 58 cases. Hence it is not possible to determine whether or not the patient with the cystic kidneys was one of the 43 who had a ruptured aneurysm. It may have been, but from the report one cannot be sure.

Rupture of the intracranial aneurysm is a common feature of most reported cases. However, 2 unruptured aneurysms were found by Fearnsides[25] in a 53-year-old man with polycystic disease who died of uremia. The aneurysm in the 13-week-old infant who died of congenital polycystic renal disease, reported by Forster and Alpers[26], was unruptured, and in 2 of the cases we are reporting from this laboratory, unruptured aneurysms were found.

Many instances of polycystic kidneys in patients who have suffered from intracranial hemorrhage have been reported. It would not be unreasonable to assume that in at least some of these rupture of an intracranial aneurysm may have been the cause of the hemorrhage. Indeed, when the relatively young age of some of the patients is considered, the likelihood of a ruptured aneurysm seems even more likely. In McKinlay's case[43], for example, the intracranial hemorrhage occurred in a 30-year-old man. Death of a 22-year-old sailor from a similar hemorrhage was recorded by McGregor[42] who also noted that the vessels of the Circle of

Willis seemed healthy. Some 7 other instances are to be found as cases or reports in the literature[7,14,18,33,46,56,66]. A compilation of statistical surveys on polycystic renal disease in association with other disorders reveals that intracranial hemorrhage was noted 38 times in 490 cases[2,4,16,19,36,57,59,70]. When single examples are added, a total of 47 cases of intracranial hemorrhage occurring in 499 patients with polycystic disease may be tabulated. This is certainly a significant number, being nearly 10% of this total of cases of polycystic kidney disease.

However, Bell[3] has considered intracranial hemorrhage to be sufficiently uncommon in polycystic disease as to be merely fortuitous. Furthermore Bell[3] and Braasch and Schacht[10] have concluded that cerebral hemorrhage occurs chiefly in those persons with polycystic disease who develop hypertension, which is a common complication[67].

Only a few statistical surveys are sufficiently detailed to permit calculation of the probable incidence of polycystic kidneys with intracranial aneurysms. In most of the studies, whether primarily concerned with polycystic renal disease, intracranial aneurysms, or cerebral hemorrhage, the analysis has usually been made in terms of the author's major concern, and other associated, presumably irrelevant, disorders are often only casually or incidentally mentioned. Thus Sahs and Keil[65], in a tabulation of 12 cases of ruptured intracranial aneurysms, make reference to polycystic disease in 2 of these cases but do not elaborate on the matter. Yet from the statistics available in 8 relevant reports[1,11,25,45,48,55,65,73] 21 instances of polycystic kidneys are found in 360 cases of congenital intracranial aneurysms, an incidence of 5.9%. The aneurysms in these 360 cases were only of congenital type since all described mycotic, luetic, or clearly arteriosclerotic aneurysms were excluded from consideration. Perhaps the inclusion of Magee's figures, based on the presence of one case of polycystic disease in 43 cases of ruptured aneurysms, is of questionable validity. If his figures are deleted, then 20 instances of polycystic disease were found in 314 cases of intracranial aneurysm, an incidence of 6.4%.

Although numerous reports have recorded the incidence of intracranial hemorrhage with polycystic renal disease, only two specifically state that the hemorrhage was due to rupture of an aneurysm. Suter[73] found 2 ruptured aneurysms in 5, and Brown[11] 6 in 36 cases of polycystic kidneys, making a total of 8 intracranial aneurysms in 41 cases of polycystic renal disease. The resulting incidence of nearly 20% is a value which is probably excessive, but of this we cannot be certain because of insufficient statistical data provided in other studies. If these two reports, which give sufficient information to permit one to make a definite statement concerning the coexistence of polycystic kidney disease and intracranial aneurysms, represent the true state of affairs, then the association of these congenital defects is certainly more than accidental and presumably stems from a fundamental genetic or embryologic abnormality.

An analysis of the cases of polycystic renal disease discovered or confirmed by necropsy at the Albany Hospital reveals a total of 18 cases in 8,882 necropsies, which gives an incidence of 1:493 (0.2%). This compares with an incidence of 1:351 (0.3%), from the combined statistics of 110,024 necropsies compiled by Bell[4]. Four of these 18 cases occurred in infants and in none of these was an aneurysm found. This is not surprising, however, since cerebral aneurysms are seldom found in infants. The only

reported case is that of Forster and Alpers[26] which is unique in that the aneurysm, in a 13-week-old infant, was also associated with polycystic kidneys. The remaining 14 patients in our series were 30 years of age or over, and of these, examination of the brain was permitted in only 6 instances. In 3 of these 6 cases, aneurysms were found. While no signs or symptoms suggesting either an intracerebral hemorrhage or a vascular abnormality were present in the 8 cases where the brain was not examined, it should be noted that in 2 of the 3 cases where intracranial aneurysms were found, clinical signs of their presence were also missing.

In this same group of 8,882 necropsies, "berry" type aneursyms were found in 47 cases. All of these were of congenital type and only 7 were unruptured. Polycystic kidneys were also present in 3 of these 47 cases (6.4%), which compares favorably with the incidence of 5.9% for the combined statistics noted above. Three patients out of 18 with polycystic kidneys, or 16.6% of those with this disease, had intracranial aneurysms, which likewise correlates closely with the combined findings of Suter[73] and Brown[11], although in only one of our patients (5.5%) was death due to rupture of the aneurysm.

Another bit of evidence suggestive of a fundamental relationship linking the congenital defects in the kidneys with those in the cerebral vasculature is the rare disorder known as Lindau's disease or Lindau-Von Hippel's (Von Hippel-Lindau's) disease. This entity is characterized by the presence of angioblastic tumors, which are often cystic, in the central nervous system and sometimes in the retina[20,34,35,38]. Multiple cystic lesions of the pancreas and kidneys, as well as other types of congenital anomalies, are so often present that Lindau[38] considered a cystic pancreas and cystic kidneys as essential elements of this abnormality. Hence this disorder may exhibit defects of several organ systems, as do tuberous sclerosis and neurofibromatosis of Von Recklinghausen. Moreover, Lindau's disease, as well as polycystic renal disease, appears to be a hereditary disorder[12,13,14,38]. It should be mentioned, though, that the cystic lesions of the kidneys found in Lindau's disease, were thought by Parkes Weber[77] to differ from those of true congenital polycystic disease, although he did not explain the nature of this difference.

Since intracranial aneurysms are associated with polycystic kidneys in a significant number of cases, it might be wondered if aneurysms elsewhere in the vascular system had been encountered. No reports of such lesions have been found. Even when injection studies of arteries supplying polycystic kidneys have been made, no suggestion of aneurysms in these vessels has been reported[30,63].

It can also be mentioned, in passing, that Schlumberger[68] observed polycystic kidneys to be a not uncommon hereditary congenital disorder in goldfish, often occurring in conjunction with neurofibromatosis.

Other Abnormalities Associated with Intracranial Aneurysms and Polycystic Kidneys. That coarctation of the aorta may be found in association with intracranial aneurysms is well known, and the association of these two lesions is generally accepted as evidence of related vascular defects. The presence of hypertension is commonly assumed to be an important predisposing factor in the rupture, and possibly the development, of intracranial aneurysms. Consequently the marked hypertension which is so often present in the carotid arterial system in cases of coarctation of the aorta, might well be a significant cause of rupture, and possibly even the develop-

ment, of a berry aneurysm in cases where the wall of the intracranial artery was already defective and weak. Actually it is difficult to evaluate the significance of hypertension with regard to the rupture or development of intracranial aneurysms, since the information given in most reports is too inadequate to permit careful appraisal. For instance, it is evident that the hypertension that may be present, surely represents an increase in blood pressure which follows intracranial hemorrhage, and that information concerning the status of the blood pressure prior to the onset of hemorrhage is often lacking[27,32,62].

A careful analysis of statistical reports reveals that coarctation of the aorta is a far less common disorder than polycystic kidney disease. Thus the number of reported instances of coarctation and associated intracranial aneurysms is not large. The incidence of coarctation of the aorta, as reported by Blackford[6], is only 1:1,500, while the incidence of polycystic renal disease is in the order of 1:351 as noted above. Nevertheless, Wright[80] was able to collect 304 cases of coarctation in which autopsies had been performed, and of these 16 had intracranial aneurysms, death being due to rupture of the aneurysm in 11 instances. A leaking aneurysm was present in one instance and unruptured aneurysms were found 4 times. Death of the patients in these latter 5 cases was due to some condition other than the aneurysm.

In the series of 8,882 necropsies performed at the Albany Hospital, coarctation of the aorta was found 5 times, an incidence of 1:1,176, as compared with 18 cases of polycystic disease of the kidneys, an incidence of 1:493. Death from rupture of the intracranial aneurysm occurred in one of the 5 cases: A brief account of this case is given herewith:

CASE 4. The patient, a 21-year-old man, was admitted to the hospital because of the onset of severe, generalized headache, convulsive seizures, and stupor. At the age of 13 a diagnosis of coarctation of the aorta had been made and since that time his activity had been restricted. Clinical evaluation in the hospital indicated the likelihood of a ruptured intracranial aneurysm but its site could not be demonstrated by angiograms. The blood pressure in the right arm was 180/100, left arm 170/90, while no pressure at all could be obtained in the lower extremities. Upon recovery from the cerebral symptoms, thoracotomy was performed and the constricted segment of aorta, located 2.5 cm. below the left subclavian artery, was resected. Post-operatively the patient had a relatively uneventful convalescence. The blood pressure in his arms stabilized at 140/100 and strong pulsations were palpable in both lower extremities. However, one month later, while going to the bathroom, he suddenly vomited, fainted, developed extensor rigidity, and died.

Necropsy, performed 11 hours after death, showed good healing of the wound in the aorta. A ruptured aneurysm measuring 1.5 by 1 by 1 cm. in size, was found at the junction of the right anterior cerebral and the anterior communicating arteries. Massive subarachnoid and intracerebral hemorrhage had resulted. The right posterior communicating artery measured less than 0.1 cm. in diameter, as compared with 0.2 cm. on the left.

One of the other 5 cases in this series was most unusual. A 17-day-old male infant had coarctation of the aorta and a patent ductus arteriosus in association with polycystic kidneys, a combination of anomalies which seems not to have been recorded previously.

Biliary cysts of the liver and cysts of the pancreas have been observed so frequently in patients with polycystic renal disease as to need little comment, cystic livers being found in about 20 to 40% of cases[4,16,37,50,57,59,70,72] while cysts of the pancreas occur less often in the neighborhood of 10%[59]. Of the 18 cases of polycystic kidneys observed in this laboratory, biliary cysts were

noted 4 times and cysts of the pancreas twice. Although Norris and Tyson believe the same type of fundamental defect that leads to the development of the cystic abnormalities of polycystic renal disease is also responsible for congenital cystic disease of the lungs[54], it seems odd that only 3 instances of associated cystic disease of both the kidneys and the lung have been recorded[11,44,55]. Cystic lesions of the spleen are occasionally noted[21,55,59], and one instance of polycystic spleen in association with polycystic renal disease is on record[29].

A few other lesions have occasionally been noted in association with polycystic kidneys. A primary intracranial neoplasm has been found 3 times. In one of our 18 cases death was due to a glioblastoma multiforme. Bell[4] noted the presence of a glioma in one of his patients, and a spongioblastoma multiforme was associated with polycystic kidneys in a case recorded by Rall and Odell[59].

Some 17 tumors of the kidneys, both benign and malignant, have been noted in association with polycystic renal disease[8,11,17,28,39,40,47,74,76,78]. Conversely, at least 3 instances of intracranial aneurysms have been reported in patients with primary renal tumors[22,58,61]. In the 47 cases of intracranial aneurysms from the Albany Hospital, cortical or retention cysts of the kidneys were present in 3 cases, biliary cysts of the liver in one, and a fibroma of one kidney in one. Cairns[13] reported a high incidence of myopia in association with polycystic disease in one family, apparently evidencing a strong familial or hereditary influence. A case of glaucoma without increased intraocular pressure with polycystic renal disease has been recorded[5]. One instance of congenital glycogenic tumor of the heart (rhabdomyoma), a disorder frequently associated with tuberous sclerosis, was reported in association with polycystic kidneys in a female infant who lived 24 hours[24].

While congenital absence of the gallbladder with polycystic renal disease is observed most commonly in the neonatal group, Zimmerman[81] records an example of the association of these two anomalies in a 70-year-old man who died from carcinoma of the head of the pancreas. It is also worth noting that congenital absence of one kidney in association with polycystic disease of the remaining organ has been recorded at least 4 times [11,15,19,60]. Yet the possibility of unilateral polycystic renal disease has often been denied[31,64].

Many of these abnormalities that have been present in association with polycystic kidneys or intracranial aneurysms may have been merely coincidental. However, as is so clearly evident in the childhood type of polycystic renal disease, it also seems possible that persons who live to adult life with polycystic renal disease may also have widespread anomalies of other organ systems, particularly the liver, pancreas, and central nervous system. Hence polycystic renal disease may actually be but one manifestation, generally, a striking and highly significant one, of a group of disseminated embryonic defects or hamartoses, somewhat similar in character to tuberous sclerosis, neurofibromatosis of Von Recklinghausen, or Lindau-Von Hippel's disease.

Summary. Intracranial aneurysms and polycystic renal disease, two congenital anomalies, occur in association with each other in a significant number of cases. The number of instances in which these two disorders have been found together suggests that more than simple coincidence is involved in this relationship. Three additional cases of the association of these two types of lesions are presented.

A brief discussion of other anomalies

found in association with either intracranial aneurysms or congenital polycystic kidneys is also made.

It is suggested that polycystic disease of the kidneys may represent one phase of a disseminated congenital disorder somewhat analogous to tuberous sclerosis, neurofibromatosis of Von Recklinghausen, or Lindau-Von Hippel's disease.

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THE ANTICOAGULANT EFFECT OF PHENYLINDANEDIONE IN THROMBOEMBOLIC DISORDERS*

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In 1944, Kabat, Stohlman and Smith[5], in the course of an investigation of the toxicity of indanediones, discovered that these chemicals produced fatal hemorrhages in laboratory animals by lowering plasma prothrombin. Three years later, Meunier *et al.*[6] reported that phenylindanedione, a less complex member of this group, also had a prothrombin depressant action in rabbits and that the effect was more transitory than that of Dicumarol. Soulier and Gueguen[9,10] confirmed the properties of this drug in rabbits and described its effects in 43 patients[3]. Further experimental studies have been conducted by Jacques[4], and further clinical trials have been made by Blaustein[1] and Preston[7]. The purpose of this report is to record additional experience gained from 143 patients treated with this drug on the public wards of the Toronto General Hospital.

In this investigation, phenylindanedione was one of 4 anticoagulants used in a comparative study in patients with thromboembolic disorders such as myocardial infarction, pulmonary infarction, phlebothrombosis, and so forth. The other drugs used were heparin, Dicumarol and cyclocumarol (Compound No. 63, or BL5). The clinical effectiveness of phenylindanedione compared favorably with the others; the details of this will be reported later. This report is chiefly concerned with the action of phenylindanedione on plasma prothrombin level.

Methods. One of the anticoagulants was assigned at random to each patient. The daily doses were ordered by the resident staff under the supervision of the authors. Clotting times (Lee-White) and prothrombin times (one-stage, Quick) were performed daily except Sundays. The prothrombin times were reported in seconds as well as a percentage of normal. This percentage was determined from a dilution curve of normal plasma prepared for each solution of thromboplastin. Prothrombin levels between 10 and 30% of normal were considered within the "therapeutic range."

Results. Speed of Effect. The usual initial dose was 200 mg., with subsequent doses depending on the prothrombin times. Figure 1 illustrates the speed with which a therapeutic effect (prothrombin level of 30% or less) was achieved in 53 cases in which prothrombin times were performed daily during the first 5 consecutive days. It will be noted that the majority of patients were within the therapeutic range by the second day. Of the 4 cases which showed an inadequate response during the first 5 days, all showed some prolongation of prothrombin time and, in 3, this subsequently reached therapeutic levels.

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The fourth case was maintained on an average dose of 100 mg. per day for 5 weeks; his prothrombin level varied between 33 and 100% of normal. Had this case been later in the series, larger doses would have been given. The daily maintenance requirement showed considerable variation from case to case, the extremes being 12.5 and 300 mg. When larger doses were administered to the less susceptible individuals, no cases of resistance, such as reported by Blaustein[1], were encountered.

in these conditions. In Fig. 2 the speed of effect in 53 cases receiving phenylindanedione is compared with 30 cases receiving Dicumarol and 30 cases given cyclocumarol.

Persistence of Therapeutic Effect. Thirty cases in which the prothrombin time was at a therapeutic level at the cessation of treatment were followed, with daily determinations, until they had risen well above the therapeutic range. The result is shown in Fig. 3. In more than half the patients the prothrombin level had risen above

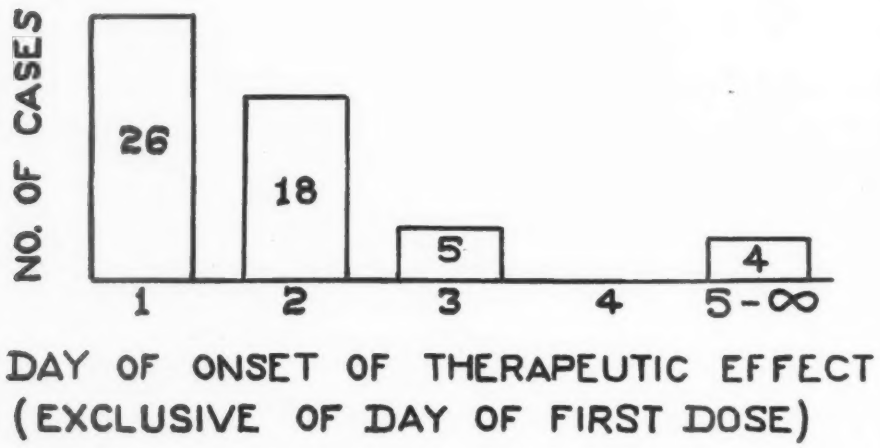

Fig. 1.—Speed of effect of phenylindanedione.

In a few patients the prothrombin level fell below 10% within the first 3 days. This marked response did not appear to be directly related to age, sex, diagnosis or initial prothrombin level. There appeared to be little acceleration of effect by increasing the size of the initial dose and frequently as rapid a response was noted to 100 as to 300 mg. This warrants further study. As noted by Stats and Davison[11] and Covert[2], patients with severe cardiac insufficiency and shock seemed to exhibit an increased response; cautious induction of therapy is recommended

the accepted range by the second day and, in virtually all, by the third day after discontinuing the drug. Furthermore, the effectiveness of phenylindanedione disappeared more quickly than that of Dicumarol or cyclocumarol (See Fig. 4).

Ease of Control. A major concern in anticoagulant therapy is the maintenance of a prothrombin level within the selected therapeutic range. Using any of the drugs now available, it is very difficult to obtain constant levels within this range as certain patients

periodically show unpredictable swings in prothrombin time.

In an attempt to assess the ease of control, 20 patients who had been treated for at least a month were selected at random from each oral anticoagulant group. The percentage of days in which prothrombin levels were in the therapeutic range during the second fortnight is shown in Table 1. Better control was obtained in patients receiving cyclocumarol or Dicumarol. Preston *et al.*[7] reported 65% of daily prothrombin determinations within the 10 to 30% range with phenylindanedione. The majority of their patients received the divided dose schedule previously reported by

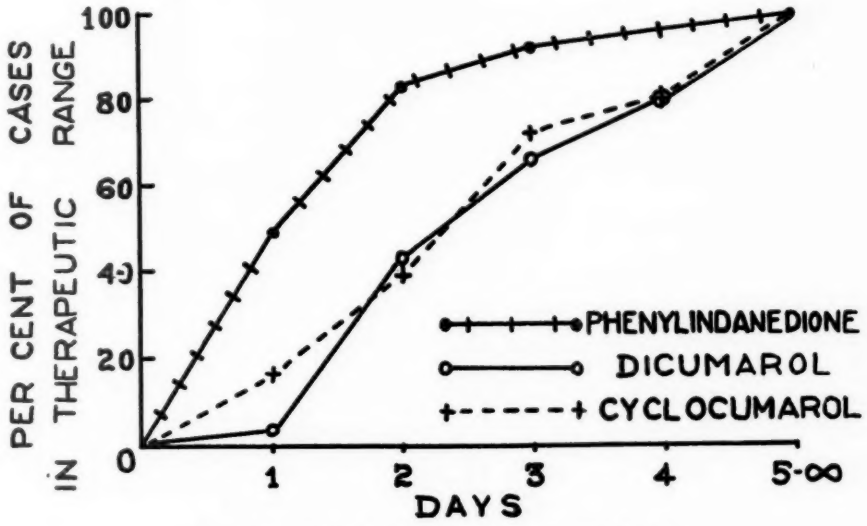

FIG. 2.—Speed of effect of oral anticoagulants.

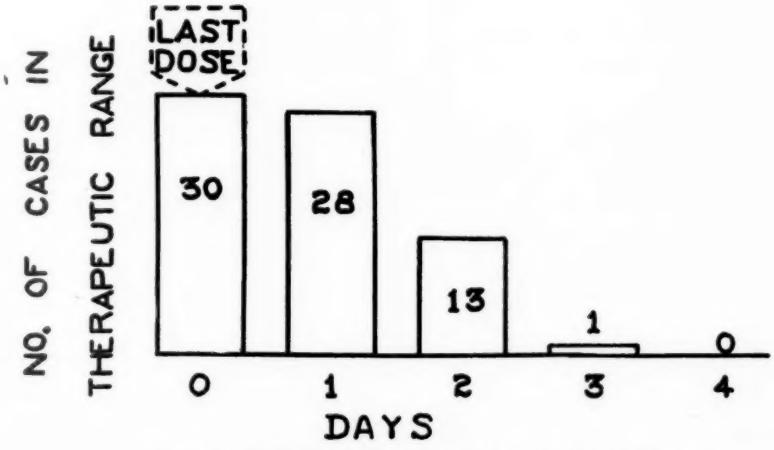

FIG. 3.—Persistence of action of phenylindanedione.

Jacques[4] and Blaustein[1] as the method achieving more constant control. The necessity of twice daily administration of a drug which requires one or two days to become effective seemed open to question. Consequently, a group of patients were given the drug in divided doses at 12-hour intervals; no better control was obtained. We attribute our less favorable control with phenylindanedione to inadequate dosage resulting from thinking in terms of the more familiar dosage schedule of Dicumarol. This view is strengthened by the observation that, in a group of private patients where single daily doses of phenylindanedione were controlled by the authors, 88% of prothrombin determinations in the second fortnight were within the therapeutic range. The average daily dose in this group was 141 mg. per day as compared with 92 mg. for the public ward series.

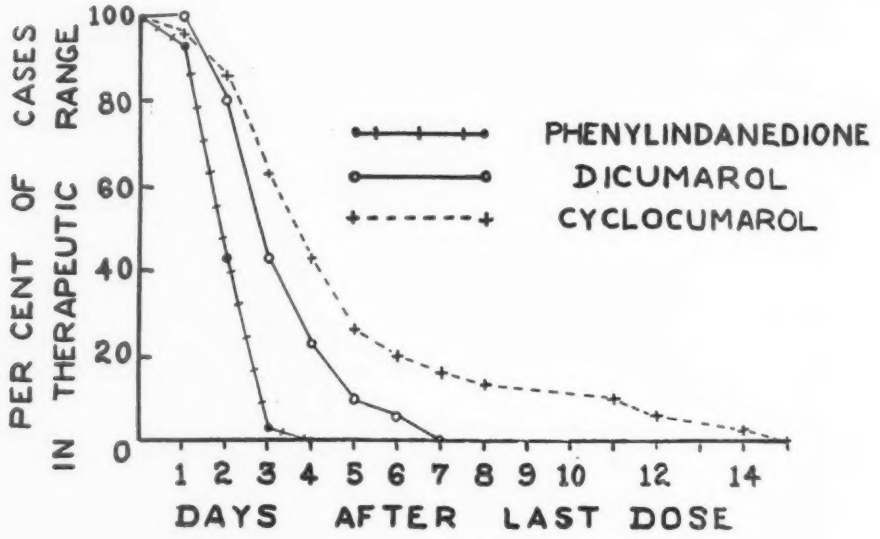

FIG. 4.—Duration of effect of oral anticoagulants. (Thirty patients on each drug)

TABLE 1.—PERCENTAGE OF DAYS DURING THE SECOND FORTNIGHT OF TREATMENT IN WHICH PROTHROMBIN LEVELS WERE IN THE THERAPEUTIC RANGE

Drug	*Prothrombin Levels in Therapeutic Range Percentage of Days*
Cyclocumarol	68.7
Dicumarol	63.0
Phenylindanedione	50.0

TOXIC REACTIONS. *Hemorrhage.* Bleeding has been comparatively uncommon in patients receiving phenylindanedione. Preston *et al.*[7], in a recent survey of the literature, found no serious hemorrhage in 274 reported cases. No gross bleeding was observed in the 143 patients in this series. Had larger doses been given to maintain more of the patients in the therapeutic range, it is quite probable that hemorrhagic complications would have occurred. Actually, in the group of private

patients previously mentioned, there were 2 instances of gross bleeding into operative incisions. The following is a brief summary of these 2 cases:

K.C., a 34-year-old woman, had undergone spinal fusion for a herniated intervertebral disc. She was given phenylindanedione 2 weeks postoperatively because of pulmonary infarction. Three months later the Kerschner wire holding the bone graft in place was removed and, 6 days later, a brisk hemorrhage occurred at this site. At the time of the bleeding, the prothrombin time was 41 seconds, the normal control being 15 seconds. The drug was discontinued and the subsequent course was uneventful.

M.J., a 50-year-old woman, had had an arthroplasty performed on her left hip because of advanced osteoarthritis. Phenylindanedione therapy was instituted 4 weeks after operation for phlebothrombosis of the left leg. On the fifth day of anticoagulant therapy, a large hematoma developed in the incision and spread forward over the thigh and backward over the buttock. The prothrombin time on the day that this occurred was 67 seconds, considerably beyond the accepted limit of safe treatment. One gram of vitamin K_1 oxide was administered orally, and no further bleeding occurred. Twenty-four hours later the prothrombin time was 17 seconds.

Vitamin K has been found ineffective in combatting the hypoprothrombinemia induced by phenylindanedione. This has been suggested as a possible hazard in the use of this anticoagulant[12]. Vitamin K_1 and K_1 oxide, however, have been used successfully and, in *earlier* trials, we observed satisfactory restoration of excessively low prothrombin levels within 4 to 5 hours after an oral dose of one gram of either of these drugs. Rehbein *et al.*[8] reported that smaller doses of vitamin K_1 emulsion intravenously were also effective, and we have confirmed this. Figure 5 illustrates the rapid fall in prothrombin time following an intravenous injection of 50 mg. of vitamin K_1 emulsion.

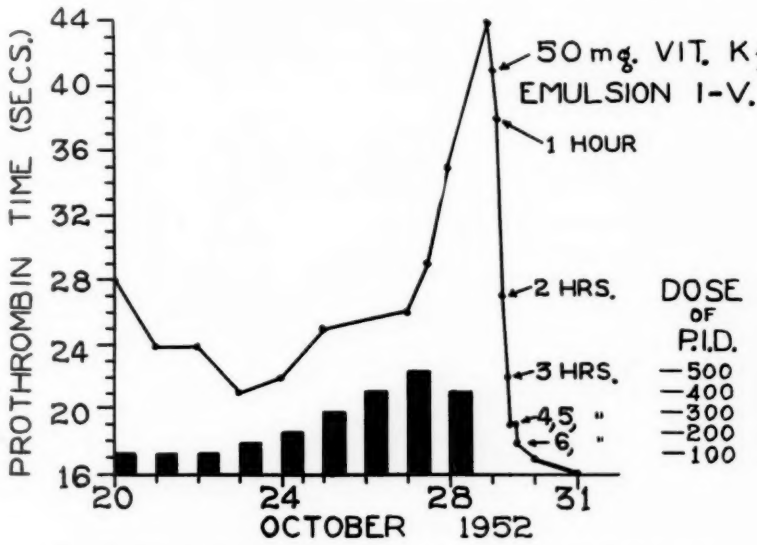

FIG. 5.—Effect of Vitamin K_1 in combatting hypoprothrominemia induced by phenylindanedione.

As reported by Soulier and Gueguen[3], dark orange discoloration of the urine was observed frequently in patients on phenylindanedione and, on

occasions, this caused some alarm to patients and nursing staff who were on the alert for hematuria. A number of urinalyses in such cases did not show any abnormality, and the color is thought to be due to an excretion product of phenylindanedione. This discoloration was much more apparent in acid urines and could be made to fade considerably by rendering the urine alkaline.

Summary. 1. Experience is recorded of the use of phenylindanedione in 143 patients with thromboembolic disorders.

2. Satisfactory depression of prothrombin was achieved in most cases in 48 hours and, when the drug was discontinued, disappeared usually in 2 days.

3. In this series the maintenance of prothrombin times in the therapeutic range was not as satisfactory as with cyclocumarol or Dicumarol. This was probably because of inadequate dosage.

4. No hemorrhage was encountered in the group reported but, in 2 private patients treated by the authors, bleeding occurred into operative incisions.

5. Vitamin K_1 and K_1 oxide are effective antidotes causing a restoration of safe prothrombin levels within 4 to 5 hours.

ACKNOWLEDGMENTS. The phenylindanedione used was Danilone (Frost & Company). Heparin was supplied by Connaught Medical Research Laboratories, Toronto. Cyclocumarol (BL5) was supplied by Abbott Laboratories Ltd. (Cumopyran, Abbott). Vitamin K_1 and K_1 oxide were supplied by Merck and Company.

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CHRONIC ATROPHIC GASTRITIS: SYMPTOMATIC PROCLIVITIES

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It is apparent that discussions of the clinical significances of the gastritides must be based largely on impressions and suppositions, because there is no clear-cut clinical method for objective evaluation. Circumstantial evidence may be the best kind of evidence in clinical medicine, as it may in juridical matters, but the impotence of clinical measuring techniques for the gastritides has led to remarkably vehement and often groundless dissension over symptomatic proclivities. It is not the intention to enter the argument at this time; however, a review of the very extensive literature impresses one with the fact that an important hiatus has been created by failure adequately to examine gastritis patients for other possible explanations for the symptomatic picture.

Material and Methods. During the last 2500 gastroscopic examinations performed on this Section, 70 instances of chronic atrophic gastritis were diagnosed. The diagnoses were based on the generally accepted criteria, namely, increased translucency of the mucosa, a peculiar pale slate-red mucosal color, highlights assuming the appearance of a diffuse sheen, and, most important, visibility of the submucosal venous channels. The 70 patients included 11 women. The number per age-decade from the second through the ninth decades were, respectively, 3, 13, 11, 10, 14, 12, 4, and 3.

The patients were hospitalized. Although the courses of objective investigation depended on the individual clinical problems at hand, all were thoroughly studied. In addition to routine examinations, all patients had stool examinations, gastric analysis, and upper gastrointestinal and gallbladder roentgenography; most had esophagoscopy, colon roentgenography, and liver biopsy and function tests; and some, surgical exploration and psychiatric evaluation.

Fifty-seven patients had been gastroscoped in a search for an explanation for upper gastrointestinal symptoms (Table 1). Among the 13 found to have atrophic gastritis but no upper gastrointestinal complaints, there were 3 who had been gastroscoped because of known pernicious anemia, 2 because of unexplained hypochromic anemia, 3 with carcinomatosis because the primary tumor had not been detected, and 5 for routine study following abdominal Roentgen-irradiation.

Findings. Completed study of the 57 patients with upper gastrointestinal symptoms revealed that 51 had other diseases which were good and perhaps better explanations for those symptoms than the atrophic gastritis (Table 2). Five patients had more than one additional diagnosis. The table also lists the upper gastrointestinal and other diagnoses which the clinician believed to be noncontributory to the symptoms under discussion. It is noted that the 70 patients had a total of 228 discharge diagnoses. Several of these were presumed to be related in some way to the gastritis: carcinoma of the stomach in 5, multiple avitaminoses in 2, thyroid disease in 2, gastric polyps in 5, chronic superficial gastritis in 14, gastric petechiae in 3, erosions in 1, hyperplastic mucosal changes in 4, and pernicious anemia in 5.

The 6 symptomatic patients whose only diagnosis was chronic atrophic gastritis had a variety of complaints. A compilation of the 2 most important symptoms per patient shows that 4 complained of complex dyspepsia, 3 of weight loss, 2 of epigastric pressure, 2 of periodic vomiting, and one of ulcer-like pain.

TABLE 1.—57 PATIENTS WITH CHRONIC ATROPHIC GASTRITIS AND UPPER GASTROINTESTINAL SYMPTOMS: COMPILATION OF THE TWO MOST PROMINENT COMPLAINTS OF EACH PATIENT, AND TABULATION OF THE DURATION OF SYMPTOMS

	Instances		*Patients*
Ulcer-like pain	17	1 month	5
Complex dyspepsia	16	2 months	3
Gas	15	4 months	8
Weight loss	15	6 months	8
Vomiting	12	8 months	2
Anorexia	10	1 year	9
Weakness, fatigue	10	1½ years	4
Epigastric cramps	7	3 years	6
Epigastric pressure	4	5 years	4
Pyrosis	4	6 years	1
Melena	2	10 years	3
RUQ pain	2	15 years	4

TABLE 2.—DISCHARGE DIAGNOSES IN ADDITION TO CHRONIC ATROPHIC GASTRITIS AMONG 70 PATIENTS, 57 OF WHOM HAD UPPER GASTROINTESTINAL SYMPTOMS: CLASSIFICATION OF DIAGNOSES ACCORDING TO APPARENT SIGNIFICANCE IN CONNECTION WITH THOSE SYMPTOMS

Probably symptomatically significant (51 patients)	*Patients*
Esophagus:	
Cardiospasm	1
Stomach:	
Carcinoma	5
Diverticulum	5
Hiatus hernia	4
Prolapse antral mucosa	2
Ulcer	4
Duodenum:	
Ulcer	4
Pancreas:	
Carcinoma	4
Chronic pancreatitis	1
Cyst	1
Liver:	
Chronic hepatitis	2
Cirrhosis	1
Gallbladder:	
Post-cholecystectomy syndrome	3
Chronic cholecystitis	5
Other:	
Giardiasis	1
Ascariasis	1
Hodgkin's disease	1
Hypothyroidism	1
Renal calculus	1
Subacute bacterial endocarditis	1
Anxiety reaction	7
Psychopathic personality	1

Probably not contributing to upper G. I. symptoms	*Patients*
Esophagus:	
Diverticulum	1
Stomach:	
Achlorhydria	47
Polyps	5
Extrinsic pressure	4
Hiatus hernia	1
Prolapse antral mucosa	1
Superficial gastritis	14
Petechiae	3
Multiple erosions	1
Hyperplastic changes	4
Duodenum:	
Diverticula	2
Other:	
Carcinoma ovary	1
Bronchogenic carcinoma	2
Parkinsonism	2
Pulmonary tuberculosis	1
Hyperthyroidism	1
Pernicious anemia	5
Chronic sinusitis	1
Post-irradiation abdomen	5
Diverticulosis coli	1

Comment. One often reads that the blame for the age-old confusion over the clinical significance of gastritis can be laid directly to that gifted Napoleonic battalion surgeon, Broussais, and his ignorance of postmortem gastric autolysis. It may be that the more modern medical philosophers, too, have been responsible for a share of the reigning confusion. It is interesting to note how vehemence of opinion has compounded itself, as exemplified in this statement[1], published in 1944, without data: "(Other authors) wrote in 1937 'chronic gastritis is a very frequent and often a severe disease'. This ridiculous assertion epitomizes the literature which has so long misled us in our search for knowledge of this obscure subject." The present writer does not know whether or not chronic atrophic gastritis ordinarily causes symptoms, but at the moment would like to be able to retract some implications in the affirmative previously expressed[10].

The results of objective investigation have frequently been of no more help to the clinician than opinion. In 1939, Lundbaek[8] published a comparison of the symptoms of patients who gastroscopically showed gastritis and patients whose stomachs appeared normal, and, finding little difference, concluded that the symptoms of gastritis are most variable. Ten years later Findley, Kirsner, W. L. Palmer and Pullman[5] repeated the study, recorded almost identical findings, and concluded, "The common types of chronic gastritis apparently produce no symptoms . . ."

There is an extensive literature based on the opinion that "primary" uncomplicated chronic atrophic gastritis is responsible for important symptoms[2,3,7,9,11]. Clinical[4] and pathologic[6] evidence to indicate that atrophic gastritis may frequently exist without causing symptoms proves nothing regarding clinical significance, nor does the commonly recorded observation that patients with this objective entity may have a great variety of subjective findings. Certainly, however, symptoms associated with demonstrated gastritis do not indicate cause and effect. If atrophic gastritis is a rather common incidental finding at necropsy[6], and if a large proportion of symptomatic patients with atrophic gastritis are found to have other major diseases of the upper abdomen, the symptomatic importance of the gastritis must be regarded at least as questionable.

It must be emphasized that this was a study of symptomatic correlations only, and that the results are not to be applied to considerations regarding pathologic significance. Chronic atrophic gastritis plays several important pathogenic roles: as a basis for depressed gastric secretory activity with all that that implies, particularly regarding iron utilization and pancreatic function, as the initial step in one form of adenomatous transformation, and as a process possibly related in some causal way to gastric carcinoma and pernicious anemia.

Summary and Conclusion. 1. Seventy patients with the gastroscopic diagnosis of chronic atrophic gastritis were given thorough clinical study in an effort to uncover coexistent disease. A total of 228 gastrointestinal or other significant diagnoses was established in the group. Thirteen of the cases of gastritis were discovered in patients without upper gastrointestinal complaints.

2. In 51 of 57 patients with atrophic gastritis and gastrointestinal symptoms, symptomatic explanations considered to be as good as or better than the gastritis were found.

3. It is concluded that, however important the atrophic gastritis may have been in the production of observed achlorhydria and the development of gastric polyps and carcinoma, it could be considered for the most part a subclinical disease in this series of patients.

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ARTERIAL HYPERTENSION AMONG INDIANS OF THE SOUTHWESTERN UNITED STATES

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MODERN research into the pathogenesis of idiopathic arterial hypertension has been ably reviewed in the past few years[15,22,23]. Consideration of the mass of data accumulated has led to the formulation of the concept of hypertension as a psychosomatic disorder resulting from the stresses and problems of everyday living reacting through an interplay of nervous, humoral and endocrine forces[42]. Accordingly, abnormal elevation of the arterial blood pressure has been incriminated as one of the penalties of an advancing dynamic culture: "hypertension is a disorder resulting from the socio-economic complexities of modern civilization and the stresses and conflicts which they impose upon man who is trying to adapt. Hypertension is, therefore, one of the prices man must pay because of his own deficiencies in coping with the environment of the civilization he has devised for himself"[23].

Students of the biology of hypertension have derived support for this integrated concept from studies of blood pressure readings in less sophisticated cultures. Nye[21] and Donnison[6] called attention to the rarity of hypertension in the African Negro; their observations, coupled with later reports of the high frequency of this disorder in the American Negro[13,34], have been cited as evidence indicting an environmental, rather than hereditary, cause. Numerous observers have commented upon the low blood pressure of the Chinese[2,5,7,8,12], while the natural history of the blood pressure of Occidentals living in China has been a source of disagreement[8]. McCay[16] found the average systolic blood pressure of natives of Bengal to be lower than that of resident Europeans. Chamberlain[3] summarized previous conflicting data of other investigators, while he, himself, noted "practically identical" average blood pressure readings in Filipinos and a group of white men. The blood pressure of Eskimos also differed little from that of a white population[7].

Shattuck's exhaustive observations in Central America[35,36] disclosed a relative hypotension among the Indians of Guatemala and Yucatan, with higher levels in mixed racial groups. Kean[10] found that 9.8% of a relatively homogeneous West Indian population living in Panama had an average systolic blood pressure of 150 mm. of mercury or above, compared to only 1.3% of native Panamanians; a like disproportion existed in the incidence of systolic hypertension in obstetrical patients drawn from these two racial groups. Marvin's studies[17] in over 2,000 consecutive hospital admissions confirmed Kean's data; the former worker concluded that "the relatively low incidence in Panamanians may be the result of the Indian blood which is found to some degree in a large majority of the Panamanian negroes". More

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recently, Taylor[40], reviewing clinicopathologic material, found diastolic hypertension (blood pressures 100 mm. of mercury or above) to be six times as common in West Indians as in Panamanians, and three times as common as in whites; there was a parallel incidence of arteriolonephrosclerosis in these three groups. In a similar evaluation of the Cuna Indians, Kean[11] was unable to discover a single instance of hypertension among 407 adult members of this tribe living in almost complete isolation on an island off the coast of Panama. Low blood pressure levels were also recorded in the Indians of Brazil[14].

Chavez[4], in discussing the distribution of the various forms of organic heart disease among 2,400 cases admitted to a cardiologic service in Mexico City, remarked that "pure hypertension is very rare among the poor and Indian population. The incidence was 2.6% and rose to only 7.3% when the arteriosclerotic cases with hypertension were added, whereas among the private patients, who were pure white or 'mestizos' with a little Indian blood, the incidence was 36.9%". In Puerto Rico, Suarez[39] reported the lowest incidence of hypertension in hospitals in county areas and those serving the native population and the indigent poor.

In certain areas of our own United States, particularly in the Southwestern states, the American Indian lives largely a reservation existence, often in patterns centuries old, still representing a fairly distinct culture separated from the complexities of modern life. References dealing with the prevalence of hypertension in the American Indian are surprisingly few. Hrdlicka[9] comments only on "a markedly slower pulse" of the full-blooded Indian. Salsbury[32] was able to tabulate only 4 cases of hypertension and one case of "hypertrophy of the heart" among 4,826 Navajos admitted to an Arizona mission hospital over a 5-year period. Because of the paucity of the available information, it was decided to attempt to assess the incidence of hypertension among American Indians admitted to a hospital dealing exclusively with their care.

Material and Methods. All data were derived from the records of the Phoenix Medical Center Hospital, Bureau of Indian Affairs, Department of the Interior, Phoenix, Arizona. The Medical Center Hospital is the general hospital facility of the Phoenix Medical Center, and receives referrals from Indian Field Service hospitals in an area comprising Utah, Nevada and Arizona, as well as patients from the Indian population of the City of Phoenix and its environs. From July 1, 1950 to June 30, 1952, the period covered by this report, there were 1,747 consecutive admissions to all services of the Medical Center Hospital. These patients were drawn from 44 different Indian tribes and are representative of the population served. Because of the notorious inaccuracy of blood pressure readings obtained by the usual sphygmomanometric method in infants and children[30,43], it was decided to limit investigation to the 1,140 patients 10 years of age and above admitted over the 2-year period. The incidence of documented hypertension was determined, using as a standard repeated "casual" diastolic blood pressure values 90 mm. of mercury and above[25]; the records of the patients so diagnosed were then selected for further scrutiny.

Results. A. INCIDENCE. By the criteria employed there were 14 documented cases of hypertension among 1,140 admissions 10 years of age or over during the 2-year period, a gross incidence of 1.2%.

B. SEX. There were 5 hypertensives among a total of 489 men, an incidence of 1.02%, and 9 hypertensives among 651 women, an incidence of 1.3%.

C. AGE. The incidence of hypertension by age and sex is given in Table I. There was a steady rise in the percentage incidence of hypertension in the combined groups from 0% during the second decade of life to 9% in the eighth decade; elevated pressures were not reported in the 3 patients over

the age of 80. The highest incidence in each sex occurred during the eighth decade, 7.4% of the males and 11.7% of the females in this age group being affected.

D. Analysis of the records of patients with hypertension. The records of the 14 cases of hypertension were then submitted to further examination (Table 2). In many instances, optimal evaluation had been precluded by the general status of the patient, and occasionally by his or her inability to remain for more detailed observation.

3. *Known Duration of Hypertension.* The approximate period of known hypertension could be determined in a little less than one-half the patients, and ranged from under one year to over 20 years. The age of onset in these 5 individuals varied from 42 to 62 years.

4. *Degree of Blood.* With one exception, a half-blooded female, all 11 patients were full-blooded Indians.

5. *Tribe.* No definite tribal predilection could be determined in this small series, the 11 patients being distributed through 7 tribes.

TABLE 1.—INCIDENCE OF HYPERTENSION IN INDIANS BY AGE AND SEX, 1950–1952.

	Males			*Females*			*Total*		
		Hypertensives			*Hypertensives*			*Hypertensives*	
Age	*Number of Cases*	*Number*	*% of Total*	*Number of Cases*	*Number*	*% of Total*	*Number of Cases*	*Number*	*% of Total*
10–19	174	0	0	165	0	0	339	0	0
20–29	77	0	0	226	0	0	303	0	0
30–39	47	1	2.1	120	1	0.8	167	2	1.2
40–49	57	1	1.7	65	1	1.5	122	2	1.6
50–59	58	0	0	35	3	8.5	93	3	3.2
60–69	48	1	2.0	21	2	9.5	69	3	4.3
70–79	27	2	7.4	17	2	11.7	44	4	9.0
80–89	0	—	—	0	—	—	0	—	—
90–99	1	0	0	2	0	0	3	0	0
Totals	489	5	1.02	651	9	1.3	1140	14	1.2

1. Three records, of one woman and 2 men, were discarded from the original group because of the presence of disorders (pre-eclamptic toxemia, obstructive uropathy and central nervous system injury, respectively,) with which hypertension may be associated as a secondary phenomenon[23,24], leaving 11 cases. Corresponding revision of the original figures (Table 3) indicates that 0.61% of all men and 1.22% of all women could be classified as suffering from primary hypertensive vascular disease.

2. *Age at Admission.* These 11 patients ranged from 35 to 79 years of age at the time of entry into the hospital.

6. *Reason for Admission.* In 8 of the patients hypertension or its sequelae was responsible for admission; in the remaining 3 individuals hypertension was either discovered following admission for an unrelated complaint or was known and asymptomatic (Table 4).

7. *Associated Disorders.* Diabetes was the most commonly associated condition and syphilis next, occurring in 36% and 27% of the patients, respectively. Syphilis and diabetes were coexistent in 2 cases, in one of whom there was a non-toxic adenomatous goiter as well. Six cases, or 54%, were uncomplicated by associated disease.

8. *Blood Pressure Levels.* Blood pressure levels ranged from 90 to

TABLE 2.—CLINICAL AND LABORATORY DATA IN 14 INDIAN PATIENTS WITH HYPERTENSION, PRIMARY OR SECONDARY*

Pt.	*Age*	*Sex*	*Tribe*	*Degree of Blood*	*Blood Pressure Readings***	*Area Involvement****				*Proteinuria*	*Anemia†*	*Diabetes*	*Syphilis*	*NPN in mg./100 cc.*	*Remarks*
						H	*B*	*R*	*K*						
BL	63	F	Ute	2/4	220/120	P	A	P	P	4-plus	P	P	A	42–60	Known duration under 1 year
AT	35	M	Walapai	4/4	200/100	P	P	P	P	4-plus	P	P	A	55–75	
RA	74	M	Paiute	4/4	250/110	A	A	P	A	Trace	P	A	A	50–55	BPH with obstructive uropathy
IW	49	F	Walapai	4/4	185/110	A	A	A	A	0	A	A	A	—	
JH	47	M	Mohawk	4/4	175/105	P	P	P	P	3-plus	P	A	A	60	Known duration 5 years. Expired in cong. heart failure
EB	37	F	Navajo	4/4	165/110	A	A	A	P	1-plus	A	A	A	40	Pre-eclamptic toxemia
WN	60	M	Apache	4/4	150/90	A	A	A	A	0	A	A	A	—	Craniocerebral trauma
WB	74	M	Chickasaw	4/4	220/100	P	P	P	A	0	A	A	A	—	Known duration 20 years. Expired following cerebrovasc. accident
NS	51	F	Pima	4/4	190/100	P	P	P	P	0	P	A	A	43	Known duration 2–3 years
EW	79	F	Tonto Apache	4/4	170/100	P	P	P	P	1-plus	P	P	P	—	Non-toxic adenomatous goiter
AS	70	F	Apache	4/4	170/90	P	A	A	P	1-plus	P	A	P	62	
DI	52	F	Apache	4/4	175/100	P	A	A	A	0	A	A	A	—	
ML	56	F	Mohave	4/4	180/100	P	P	P	P	1-plus	A	A	A	—	Known duration 10 years
MN	67	F	Pima	4/4	230/120	P	P	A	P	4-plus	P	P	P	55	Expired in cong. heart failure

* P indicates that the abnormality was present, and A that it was absent.
** Because of space limitations, blood pressure readings are the averages of two or more determinations corrected to the nearest 5 mm. of mercury.
*** H represents cardiac, B cerebral, R retinal, and K renal area involvement.
† Anemia was considered to be present when hemoglobin levels of 10 gm./100 cc. or below were recorded.

TABLE 3.—INCIDENCE OF PRIMARY HYPERTENSION IN INDIANS BY AGE AND SEX, 1950–1952

	Males			*Females*			*Total*		
		Hypertensives			*Hypertensives*			*Hypertensives*	
Age	*Number of Cases*	*Number*	*% of Total*	*Number of Cases*	*Number*	*% of Total*	*Number of Cases*	*Number*	*% of Total*
10–19	174	0	0	165	0	0	339	0	0
20–29	77	0	0	226	0	0	303	0	0
30–39	47	1	2.1	120	0	0	167	1	0.6
40–49	57	1	1.7	65	1	1.5	122	2	1.6
50–59	58	0	0	35	3	8.5	93	3	3.2
60–69	48	0	0	21	2	9.5	69	2	2.8
70–79	27	1	3.7	17	2	11.7	44	3	9.0
80–89	0	—	—	0	—	—	0	—	—
90–99	1	0	0	2	0	0	3	0	0
Totals	489	3	0.61	651	8	1.22	1140	11	0.96

TABLE 4.—REASON FOR ADMISSION IN 11 INDIAN PATIENTS WITH PRIMARY HYPERTENSION

A. Hypertension or Its Sequelae Responsible for Admission—8 patients

1. Congestive Heart Failure	4 patients
2. Cerebrovascular Accident	1 patient
3. Epistaxis	2 patients
4. Severe Headache	1 patient

B. Hypertension Discovered on Admission for an Unrelated Complaint or Known and Asymptomatic—3 patients

1. Bronchiogenic Carcinoma	1 patient
2. Repair of Ventral Hernia	1 patient
3. Treatment of Lacerations	1 patient

150 mm. of mercury diastolic, and from 150 to 250 mm. of mercury systolic. Initial values were lowest in the 2 patients admitted because of epistaxis, but rose following restitution of blood loss. Lability was characteristic of blood pressure determinations in individual patients.

9. *Symptoms and Signs.* Table 5 summarizes pertinent items in the history and physical examination of these 11 Indians with primary hypertensive vascular disease. With a single exception these patients were symptomatic and exhibited the stigmata of their disease. The coronary arterial syndromes, cardiac decompensation, cerebrovascular accidents, retinal disorders and renal insufficiency were all

TABLE 5.—SYMPTOMS AND SIGNS IN 11 INDIAN PATIENTS WITH PRIMARY HYPERTENSION*

None	1**
Headaches	7
Hypertensive Encephalopathy	1
Cerebrovascular Accidents	2
Retinal Hemorrhages, Exudates or Papilledema	1
Retinal A–V Nicking	7
Epistaxis	2
Increase in Heart Size	9
Congestive Heart Failure	6
EKG Changes	6 (of 7)
Abnormalities of Urine or Renal Function	6
Elevation of NPN	6 (of 6)

* Modified from Perera[25]

** Expressed as number of patients having the particular finding.

prominent features. All 4 of the diabetic hypertensives exhibited the clinical manifestations commonly associated with the Kimmelstiel-Wilson lesions[31]. For the entire group, cardiac area involvement was tabulated in 90%, retinal and cerebral changes in 63% each, and renal effects in 54%.

10. *Laboratory Examination.* Anemia (63%), proteinuria (63%), hyperglycemia and glycosuria (36%), and a positive serologic reaction of the blood (27%) were frequent laboratory findings. Elevation of the nonprotein nitrogen in the blood was present in all 6 instances in which it was determined.

11. *Cause of Death.* Three patients (27%) expired while under hospital observation, 2 in intractable congestive heart failure, and the third following a cerebrovascular accident.

Discussion. There is considerable difficulty in surveying the incidence of a disorder such as hypertension in which even the methods of measurement[1,29,38] and the definition of abnormality[18-20] are subject to disagreement. Further, normal blood pressure readings recorded after periods of prolonged bedrest, fever, non-specific operative procedures, myocardial infarctions or cerebrovascular accidents may obscure true hypertension[25,26,28]. However, if the criteria in a particular study are well defined and their limits rigorously observed, statistics of different investigators can be rendered comparable. Consequently, we feel that the data assembled in this report may be of some interest.

TABLE 6.—PREVALENCE OF HYPERTENSION AMONG 1,140 INDIANS AS COMPARED WITH THE INCIDENCE IN A NON-INDIAN POPULATION,* USING A DIASTOLIC BLOOD PRESSURE 90 MM. OF MERCURY OR OVER AS INDICATIVE OF ABNORMALITY

	Percentages			
	Males		*Females*	
Age	*Indian*	*Non-Indian*	*Indian*	*Non-Indian*
10–20	0	7.0**	0	3.2**
20–24	0	10.0	0	5.6
25–29	0	12.7	0	6.2
30–34	0	14.6	0	10.0
35–39	4	20.8	2	14.8
40–44	0	22.7	0	18.0
45–49	3.1	26.3	4	27.0
50–54	0	32.1	8.3	37.4
55–59	0	34.7	9.0	33.7
60–64	5.5	38.7	7.6	39.3
65–69	0	***	12.5	***
70–74	11.1		9.0	
75–79	0		6.6	

* Non-Indian population drawn from Master's studies[18] in industrial workers
** No data given by Master below age 16
*** No data given by Master above age 64

It has been estimated that about 5% of the adult population of the United States is afflicted with hypertensive vascular disease[25]. More detailed information may be derived from certain of the data of Master and associates[18] recorded in a survey of more than 15,000 industrial workers, calculated using a definition of hypertension identical with that of this study. Since none of Master's subjects were examined further, they may be considered roughly comparable to the Indian pa-

tients of our series prior to the differentiation of the latter into cases of primary and secondary hypertension (Table 6). Although the size of the 2 groups differs, the absence of hypertension in the Indian patients before the age of 35, as contrasted with a substantial percentage in the same age groups in the industrial population, is noteworthy. Among Indians of both sexes at all ages hypertension was less common than in Master's subjects, "the great majority of whom were of the white race". The overall incidence of hypertension in the 1,140 Indian admissions was 1.2%, a figure much below Perera's previously quoted estimate for the general population. When cases of secondary hypertension are excluded, the incidence of the primary variety in the American Indian drops to below 1% (0.96%) and may well have been lower had a more exhaustive evaluation been possible. The discrepancy between our data and those of Chavez[4], dealing with a similar ethnic group, may be explained by the fact that the figures of the latter investigator represent the incidence of hypertension among a relatively select group of patients, namely, those admitted to a cardiologic service, whereas our own material was drawn from patients admitted to all services of a general hospital. Our figures may be a more representative estimate of the incidence of this disorder in the general Indian population, although they are still subject to the criticism that they represent data compiled from a selected population.

Although detailed statistical analysis of these few cases of hypertensive vascular disease among American Indians is of limited validity in view of the small size of the group, certain qualitative observations can be made. As in a white population[18] hypertension was more common in women than in men, with the greatest difference between the two occurring from the fifth decade onward. The infrequency of primary hypertension before the age of 40 in the Indians studied is in striking contrast to the growing conviction that "hypertensive vascular disease can be detected in early adult life in the majority of instances"[25,26,28]. Diabetes mellitus was associated with hypertension in four instances; accordingly, hypertension was recorded in 11% of all diabetics admitted over the two-year period, a percentage closely resembling that in a non-Indian diabetic population[28]. Blood pressure levels were distributed over a wide range of elevated readings and were subject to the liability noted in other groups of patients.

As in whites, the majority of Indian patients with hypertension were troubled with complaints which could be related to their disorder. The high incidence of cardiovascular, cerebral, retinal and renal involvement parallels that observed in patients followed in the hypertension clinic of a large eastern medical center[25,26,28].

It would, therefore, appear that hypertension is as uncommon in the Indian of the Southwestern United States as it is among his cousins of Old Mexico, Central and South America, but when it does occur, little but age of onset distinguishes it from the disease in non-Indians. Admixture with other racial stock cannot be implicated in these few instances of abnormality reported here since, with a single exception, all of these patients with hypertension were full-blooded Indians.

Generations of chronic electrolyte deprivation in the arid Southwest, nutritional inadequacies, prolonged exposure to high environmental temperatures, and "a well-balanced nervous system which protects him from

the ordinary impacts of life"[4], may singly or in combination explain the freedom of the American Indian from hypertension, or as yet undiscovered factors may be responsible. Certainly more detailed observations of these people and especially of the few among them in whom the "protective" mechanisms seem to have failed may prove profitable to those interested in the basis of hypertension.

Summary. 1. An attempt was made to determine the prevalence of hypertension among 1,140 American Indians of both sexes, aged 10 years and above, admitted over a two-year period to a medical center in the Southwestern United States dealing exclusively with their care. Hypertension was considered to be present if repeated "casual" diastolic blood pressure values of 90 mm. of mercury and above were obtained.

2. There were 14 patients with hypertension among these 1,140 admissions, an incidence of 1.2%. When cases of secondary hypertension were excluded, the corrected incidence of the primary disorder was 0.96%.

3. Hypertension was somewhat more common in Indian women than in Indian men.

4. No instance of primary hypertension was noted among Indians before the age of 35, and only one case before the age of 40. Hypertensive vascular disease in the Indians studied seemed predominantly an affliction of middle and later life.

5. Clinically hypertensive vascular disease among Indians differed only in the age groups affected from the picture seen in non-Indian patients followed by other observers.

6. Attention is directed to the rarity of hypertensive vascular disease in the Indian of the American Southwest, and it is suggested that detailed studies of this culture may provide insight into the problem of hypertension.

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VARIANTS OF "MARCH HEMOGLOBINURIA"

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The clinical syndrome of "march hemoglobinuria" is characterized by hemoglobinemia and hemoglobinuria in certain young adult males following marching or running. It was first described by Fleischer[4] in 1881. Several German authors observed patients with the syndrome among troops in World War I. Additional patients were studied as soldiers of the Allied Armies in World War II by military physicians of this country and the United Kingdom[2,5,8,10]. Since 1881, approximately 76 patients have been reported. An extensive study of the subject may be found in the excellent paper of Gilligan and Blumgart, published in 1941[7].

In the past, the syndrome has almost always been related to exercise performed in the erect posture, such as marching or running. The presence of a lumbar lordosis or the assumption of a lordotic posture during the exercise has been found to be a contributory factor in many of these cases[7,12]. Spectroscopic studies of the urine after exercise, have shown that the brownish-red color is due to the presence of oxyhemoglobin. Rarely have significant numbers of red blood cells been seen[2,7].

Recently we have studied 2 patients who presented variations of this syndrome. The disturbance in one of our patients was unusual in that he developed hemoglobinuria following exercise in the horizontal position. The other's disease was remarkable in that large numbers of intact red blood cells were found in the urine concurrently with the free hemoglobin.

Case Reports. Case 1. This 22-year old single white soldier entered the U. S. Army Hospital, Fort Dix, N. J. on 15 September, 1951. The chief complaint was passing brownish-red urine after crawling through the infiltration course. He had experienced two similar episodes 2 months prior to entering the service.

He stated that he had previously been in good health except for mild hay fever every fall since childhood. In July, 1951, while swimming, the patient noted the onset of a dull aching pain in the right lower quadrant. This persisted after leaving the water and was associated with generalized discomfort. About 6 hours later he passed brownish-red urine. This was not associated with dysuria, frequency, or passage of stones. That evening he developed a chill and a dull aching pain across the back in the region of the costo-vertebral angles. The urine continued to be brown in color throughout the night, but gradually became normal after he awakened the next morning. He felt perfectly well approximately 14 hours after the

onset. As he recognized no untoward effects from this episode, the patient ignored these symptoms. One week later he again went swimming and the episode recurred. Brownish-red urine appeared approximately 4 hours after the exercise and was associated with right lower quadrant pain. He again felt poorly. These symptoms persisted throughout the night and disappeared the following morning. On both occasions the weather was very warm, and he does not recall being chilled in the water. In August, 1951, he was inducted into the Army and a few days later, while bending and lifting many heavy refuse cans, his abdomen again began to feel "strained," and the right lower quadrant pain recurred. This was followed a few hours later by passage of brownish-red urine, which again disappeared after approximately 14 hours. Another episode, very similar to this, occurred in September, 1951, following 4 hours of only moderate physical activity on the firing range. During this period the patient was bending frequently, and lying prone much of the time. On the morning of admission his unit crawled through the infiltration course which involved dragging his body in the prone position for 100 yards and passing over and under various obstacles. During this maneuver he again developed right lower quadrant pain and severe weakness. Immediately after finishing the course he passed brownish-red urine and had 2 attacks of syncope on standing upright. He was brought immediately to the hospital.

There was no past history of kidney disease, hematuria, nocturia, dysuria or passage of urinary calculi. Systemic review was not remarkable except for the existence of nasal allergy to various pollens and inhalants. This had been treated by hyposensitization injections for approximately 6 years with fair results. He also used pyribenzamine and benadryl, 4 to 6 tablets per day during the summer and fall months. He denied their use immediately prior to the episode of dark urine. An appendectomy had been performed at age 13.

The family history revealed that the father had had intermittent episodes of "bloody urine" in childhood, over a period of 2 years. These subsided spontaneously and caused no disability. He was never studied by a physician for this trouble.

Physical examination was done immediately following admission. The patient appeared prostrate. The weight was 82.6 kilograms. The blood pressure was 130/80, pulse 100 and temperature 98.6°. Physical examination was within normal limits except for slight tenderness on deep palpation in the region of a right pararectus appendectomy scar. Percussion or pressure over the costovertebral angles did not elicit pain. The prostate was normal in size and consistency. The penis was normal and circumcised.

Laboratory data included the following. Urine immediately after admission was brown and cloudy in appearance. It was acid in reaction. The specific gravity was 1.012, reaction for albumin 3+, and no reducing substance was present. Microscopic examination revealed 3 to 5 granular casts per high power field in the centrifugated sediment, but no red or white blood cells were seen. The benzidine test for occult blood was 4+. One day after admission, the urine was yellow and clear, acid in reaction, with a specific gravity of 1.021, and negative for albumin. The microscopic examination revealed only 1 or 2 white blood cells per high power field in the sediment after centrifugation.

During the period of hospitalization the following laboratory studies were performed. Many of the studies were repeated frequently during hospitalization and did not change significantly.

The erythrocyte count was 4,860,000 per c.mm., the hemoglobin 14.0 gms. per 100 cc. the hematocrit was 45% and the reticulocyte count 1.1%. The leukocytes numbered 8,550 per c.mm., with a normal differential. There were 260,000 platelets per c.mm. The blood urea nitrogen level was 7.0 mg. per 100 cc. The erythrocyte osmotic fragility test was normal. The bleeding time (Ivy method) was 1 minute and 45 seconds and the coagulation time (Lee-White) was 14 minutes. The total serum protein was 6.0 gm. per 100 cc., with albumin 3.2 gm., and globulin 2.8 gm. The A/G ratio was 1.1. The total serum bilirubin level was 0.4 mg. The serum iron level was 62.1 mcg. per 100 cc., with the total iron binding capacity of the serum being 312.0 mcg. per 100 cc. An attempt was made to demonstrate an abnormal type of hemoglobin by control alkaline denaturization of the hemoglobin as described by Singer. A normal level of 0.37 gm. per 100 cc. was present. The Coombs test was negative, as were the Donath-Landsteiner reaction and the cardiolipin microflocculation reaction. Phenolsulfonphthalein was injected intravenously and was excreted in the urine as follows: 31% in 15, 55% in 30, 71% in 60 and 85% in 120 minutes.

The patient was exercised for one hour in a prone position. The blood pH before exercise was 7.35 and after the activity the pH was 7.33. The serum sodium was 153 mEq./L. before exercise and fell very slightly to 147

mEq./L. The serum potassium was 4.8 mEq./L. before and after the exercise.

This patient was given 2 microcuries of radioactive Fe_{59} by mouth with 0.5 mg./Kg. carrier iron on January 31. On February 13th, it was found that he had absorbed, and incorporated into his erythrocytes, 16.2% of this material. The radioactivity of the patient's plasma before and after exercise was determined and from the hematocrit and plasma volume (Evans-blue dye method), it was calculated that he hemolyzed 29.3 cc. of packed erythrocytes. In a 36-hour urine sample collected immediately after exercise, we could account for the hemoglobin of 9.46 cc. of packed erythrocytes by measuring the radioactivity of the total urine volume.

The accuracy of these studies is obviously dependent upon two factors quite difficult to control. All calculations are based on the total blood volume as determined by the Evans-blue dye method. The possible errors involved in this method are well known. The second disturbing feature is the procedure of calculating the hemoglobin content of the plasma by using radioactive iron. A small amount of hemolysis in the specimens would invalidate the results. However, our findings appear to be in keeping with those reported by others and are of interest in that only a very small fraction of the erythrocyte mass is destroyed during the hemolytic attacks. The larger part of the liberated hemoglobin is retained by the body.

A roentgenogram of the chest revealed no significant abnormality. The lumbosacral spine was studied and there was no osseus abnormality or abnormal curvature. Retrograde pyelograms were made, and the kidneys, ureters, and urinary bladder were found to be normal. There was normal renal descent in the erect position. The study was repeated 2 months later and revealed no abnormalities. An intravenous pyelogram revealed the kidneys to excrete the dye promptly and in good concentration. No abnormality was visualized.

On the second hospital day there was no evidence of hemoglobin or other abnormalities in the urine. The patient appeared perfectly well with no malaise or right lower quadrant tenderness. He was later sent on 5-mile marches on two separate occasions and failed to suffer any untoward reaction. Urinalyses immediately after these marches were negative for hemoglobin, albumin and blood cells. However, one hour's exercise in a horizontal position on a table (performing simulated swimming, forward and backward bending exercises, leg raising, frog kicks and situps) caused the complete reappearance of the syndrome. The right lower quadrant pain appeared immediately and brownish-red urine was passed approximately 4 hours later. Urinalysis at that time revealed a 4+ reaction for occult blood with the benzidine test, and no red blood cells in the centrifugated urine specimen. These exercises in the horizontal position were repeated on two occasions and the findings occurred as before. An attempt was made to induce the syndrome by placing the patient in a lordotic body cast and marching him 5 miles in this position. This procedure failed to cause hemoglobinuria. An attempt was made to prevent the occurrence of hemoglobinuria by placing the patient in a kyphotic body cast, thereby preventing the assumption of a lordotic position during exercises in the prone position. Hemoglobinuria still occurred under these conditions. On another occasion cystoscopy was performed immediately following exercise in the horizontal position. The urine collected from each ureter by catheters was brown and cloudy. Microscopic examination of these specimens revealed one to two red blood cells per high power field. This finding was attributed to the minimal trauma of the catheters. The benzidine reaction on the supernatant urine was strongly positive.

The patient was observed continuously from September, 1951, until March, 1952. He performed standardized exercises in the horizontal position on several occasions during this time, and each period was followed by the appearance of hemoglobinuria. In March, 1952, he was given 25 mg. of ACTH in a slow intravenous infusion of 5% glucose in water, over a period of 10 hours. After 24 hours he was again given the standardized exercises in the horizontal position. The urine was examined for a 12 hour period following the exercise. There was no evidence of hemoglobinuria or other abnormal findings in the urine. The exercise test was repeated one week later and again 2 months later, but the syndrome did not reappear. He was returned to duty, and as of August, 1952, had not had any recurrences.

Case 2. This 24-year old white male entered the U. S. Army Hospital at Fort Dix, N. J., on 5 November 1951 complaining of intermittent "bloody urine" for several weeks prior to admission. The first episode consisted of the passage of red urine one evening about 8 weeks prior to admission. Several hours later the urine was again of normal color. The patient was unable to recall what his activities had been during that day and he felt otherwise well. The urine then remained clear for 2 to 3 weeks. He then

spent one day doing a great deal of walking, standing and bending, and that evening the urine was again red in color on two consecutive occasions. The next morning his urine was normal in color. He then reported to sick call. Cystoscopy and retrograde pyelography were done on 11 September 1951 in the out-patient clinic. There were no abnormalties found. The urine then remained clear until 6 days prior to admission when he again passed red urine after a 7-mile march. The urine remained red for several hours, and a specimen of the urine was found to contain many red blood cells. He was then admitted to the hospital for further study.

Physical examination on admission revealed the height to be 5 feet 9 inches, weight 162 pounds, pulse 68, temperature 98° and blood pressure 130/90. There were no abnormalities found.

The routine laboratory studies were within normal limits. The hemoglobin at the time of admission was 14.5 gm., red cell count 4,990,000, and hematocrit 45%. During the following 11 months of observation, in and out of the hospital, these values remained essentially unchanged. Routine urinalyses in the absence of exercise were within normal limits on many occasions, and the specific gravity was as high as 1.028 on random specimens. Urinalyses immediately after exercise in the form of 5-mile marches consistently showed many fresh red blood cells, and a brown supernatant fluid. Sometimes the urine was grossly bloody and during the first few months of observation there were less than 25 red blood cells per high power field in the sediment of a noncentrifugated specimen. Benzidine tests on the supernatant fluid were positive for several hours after each exercise period. It is realized that this test is so sensitive that it would be positive simply due to hemolysis of a few of the red blood cells present in the urine. Unfortunately it was not possible to do other studies on the supernatant fluid. The brownish color of this fluid would seem to indicate that hemoglobinuria was present in addition to hematuria.

The phenolsulfonphthalein test showed 36% excretion of the dye in the first 15 minutes and a total excretion of 64% in 2 hours. The urea clearance was 91% of average normal function. The blood urea nitrogen was 11 to 12 mg. per 100 cc. on separate occasions several months apart. The serum total protein was 6.7 gm., with 3.9 gm. albumin and 2.8 gm. globulin. The total serum cholesterol was 278 mg. per 100 cc. A Papanicolaou smear of the urine sediment was negative. No acid-fast bacilli were present in smears of urine concentrates and none were isolated by culture. The serum iron was 82.5 mcg. per 100 cc., and the iron binding capacity of the serum was 282 mcg. per 100 cc. The alkaline denatured hemoglobin was 0.3 gm. per 100 cc. by the method of Singer. The total serum bilirubin was 0.4 mg. The erythrocyte osmotic fragility was normal. The Donath-Landsteiner test was negative. On another date the serum iron was 81 mcg. before the patient was exercised. After a 5-mile hike, this had dropped to 66 mcg. The blood plasma sodium before exercise was 157 mEq./L. and after exercise was 144 mEq./L. The blood plasma potassium before exercise was 5.6 mEq./L. and after exercise was 4.6 mEq./L. Electrocardiograms were within normal limits.

The chest films were clear. Films of the lumbosacral spine showed a minimal scoliosis of the lumbar spine with the convexity to the right. Retrograde pyelograms on 11 September 1951 and again on 22 April 1952 were within normal limits. Cystoscopy was also done on each of these occasions and was also within normal limits. At the time of these examinations urine specimens were taken from each ureter. The sediment of each of these was free of cells and the specimens were sterile. On another occasion, the ureters were catheterized about 2 hours following a 5-mile hike. The urine had been grossly bloody immediately following the hike, but at the time of catheterization the sediment from both ureters contained no cellular elements. The benzidine test was positive. From the time that the patient was first under observation until July, 1952, he was sent on 5-mile hikes at intervals approximately 1 month apart. Immediately following this exercise during the first few months of observation, he developed gross hematuria and what appeared to be significant amounts of free hemoglobin in the supernatant fluid.

As time progressed, the amount of blood present following exercise gradually decreased until in July, 1952, the centrifugated urine sediment, immediately after exercise, contained only 2 or 3 red blood cells per high power field. On 1 October 1952, however, 10 to 15 red blood cells were again present per high power field in a centrifugated sediment taken immediately after exercise. No hemoglobinuria was present. No red cells had been present just before this hike. At the point when the post-exercise urine contained about 25 red cells per high power field before centrifugation, the free hemoglobin in the supernatant fluid disappeared and has not reappeared. The patient

has remained clinically well during this time. During the first few months the patient complained of mild abdominal cramps and backache during exercise, but in the last few months all of these symptoms were absent.

This patient was given an oral dose of Fe_{59} and in 14 days he had incorporated 13.6% of the dose into his total hemoglobin mass. After a period of marching the urine was collected for 36 hours and was found to contain intact erythrocytes as well as free hemoglobin. Adequate determinations of plasma hemoglobin could not be made because of slight hemolysis involved in taking the specimens.

We believe that this patient represents a variant of march hemoglobinuria for the following reasons. Hematuria or hemoglobinuria never occurred in the absence of exercise, but invariably occurred following marching or running during a period of observation of one year. No other specific cause of hematuria or hemoglobinuria could be demonstrated during this time. We were unable to quantitate the amount of hemoglobin excreted, but the deep brownish color of the supernatant urine, which was present immediately after exercise and after careful handling of the specimens, indicated that the hemoglobinuria present could not be attributed simply to hemolysis occurring after urination.

Discussion. The physiological basis of this mild form of hemolytic process is unknown, although the relationship to exercise in the erect posture has been previously well established. Certain types of exercise in the erect posture, such as wood chopping and arm exercises which involve an energy expenditure equal to, or greater than, that which would otherwise cause the syndrome by marching, have been found to have no effect on these patients. One exception was a patient reported by Witts[12], who had hemoglobinuria after bicycling as well as marching. One patient is also mentioned by Fleming[5], in whom the syndrome developed following crawling through an infiltration course in the prone position, as well as after marching.

A relationship between the syndrome and the presence of lumbar lordosis has been postulated in view of the fact that lordosis has been found to be a common structural deformity in these cases[7,12]. In those in whom it cannot be demonstrated by Roentgenray, it has been suggested that they may assume an abnormal posture which exaggerates the lumbar curve during the erect exercises. In two cases the obliteration of the lumbar curve and the production of a slight kyphosis by the application of a kyphotic body cast prevented the development of hemoglobinuria after an amount of exercise which would otherwise have produced an attack[7]. The kyphotic body cast not only prevented the appearance of hemoglobinuria after exercise but also prevented an increase in the plasma hemoglobin, which could otherwise be demonstrated in all of these cases. Our first patient developed hemoglobinuria only after exercise in the horizontal position, such as swimming and crawling. Marching, running and other forms of exertion in the erect position did not cause the syndrome. A lordotic body cast worn during a forced march had no further effect in inducing the syndrome in this patient. The wearing of a special kyphotic body cast failed to prevent the development of the syndrome during the performance of exercise in the horizontal position. The mechanism by which lordosis contributes to the hemolysis is not understood, as local hemolysis in the renal vascular system due to "passive congestion" cannot be demonstrated[7]. However, that there is a lowered renal threshold to the hemoglobin in these cases seems to have been fairly well established by the observation that the excretion of intravenously injected hemoglobin in solu-

tion occurs at lower plasma levels in patients with this syndrome than in normal persons[6,7]. Our first case suggests that exercises in the erect posture and the lordotic position are not necessary features of the syndrome as previously described. The case which Witts[12] described also could not easily have assumed a lordotic position while bicycling.

A physiological increase in plasma hemoglobin has been reported in 9 of 21 cross-country runners and in 18 of 22 marathon runners on completion of their races[7]. The mechanism by which exercise causes hemolysis is not known, since mechanical fragility and acid fragility are not increased. Hyperventilation without any specific exercise does not precipitate the syndrome[7]. The amount of blood hemolyzed during the period of exercise is small and was estimated by Gilligan and Blumgart[7] to be about 40 cc. in their cases. We attempted to measure the amount of hemolysis by giving radioactive iron orally and allowing time for the Fe_{59} to be incorporated into circulating erythrocytes. The radioactivity of the plasma and urine was then measured before and after exercise. In our first patient it was calculated that about 65 cc. of whole blood, or 29 cc. of packed erythrocytes, were hemolyzed. About one-third of the released hemoglobin appeared in the urine. The results of these calculations in the second patient are not reliable, due to the development of a slight amount of hemolysis in the blood specimens and to the presence of significant numbers of red blood cells in the urine.

Due to the successful treatment of certain types of acquired hemolytic anemia with adrenocorticotropic hormone, we attempted to study the effect of this drug on our first case. On the day following administration of 25 mg. of ACTH, the patient was exercised in the horizontal position, but no hemoglobinuria resulted. Until this time, the syndrome could be reproduced at will. Since the administration of the drug it has not been possible to induce the attacks, and none have occurred spontaneously. Thus far, no abnormal agglutinins have been demonstrated in the syndrome of "march hemoglobinuria". One can only conjecture whether the remission occurring in our single case was due to the adrenocorticotropic hormone or was merely a spontaneous recovery. The answer to this problem must await the use of the drug in future cases.

Summary. Two variants of the syndrome of "march hemoglobinuria" have been presented and discussed. The first patient developed the syndrome only after exercise in the horizontal position, thus indicating that exercise in the erect position with a lumbar lordosis is not an essential feature of the syndrome. The second patient had significant hematuria as well as hemoglobinuria after marching. The amount of whole blood hemolyzed was determined to be 65 cc. by employing a method using radioactive iron. Complete remission occurred in one case, after 7 months of observation, immediately following adrenocorticotropic hormone administration. No conclusions as to the effectiveness of ACTH can be drawn from this isolated case in a condition in which spontaneous recovery after similar periods of time is known to occur.

Addendum. After submission of this paper, Case 1 developed a spontaneous recurrence of hemoglobinuria on 23 December 1952. Prior to this time, he had been in apparent remission for 9 months after ACTH, performing exercise in all positions without hemoglobinuria.

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A BEDSIDE METHOD FOR DETERMINING THE SERUM CHLORIDES AS AN AID IN DETECTING THE CHLORIDE DEPLETION SYNDROME IN PATIENTS RECEIVING MERCURIAL DIURETICS

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An increasing number of instances of the low salt syndrome have been reported in patients receiving mercurial diuretics[5,10,15]. A simple clinical method for alerting the clinician to the presence of this syndrome has been described recently by one of us[13,14]. Briefly, the method depends upon observing the response of the urinary chlorides to a test dose of mercurial diuretic. Normally, the diuresis obtained following a mercurial diuretic results in a profuse excretion of chlorides accompanied by a brisk loss of body weight. If, on the other hand, a depression of the urinary chlorides is observed unaccompanied by a loss of weight, the low salt syndrome should be strongly suspected. To test the urinary chlorides, the Fantus test[6], recently modified by Bryant and his coworkers[4], is used. The test has been found to be reasonably accurate for clinical purposes. There are occasions, however, when it is impractical to depend solely on urinalyses such as may occur, for example, in an uncooperative patient or in an emergency situation when a sample of urine is not available. It should be pointed out that patients with the low salt syndrome develop all kinds of psychic disturbances varying from irritability and depression to frank coma[5,10,15]. A rapid easy method for determining quantitatively the serum chlorides in this type of patient obviously has certain merit.

It is the purpose of this paper to present a simple, rapid bedside method, without recourse to complicated equipment, for estimating the serum chlorides. The chlorides are examined and expressed quantitatively in the same manner as was described for the study of urinary chlorides[4,6,13,14].

Technique. A kit containing a test tube, a dropper, a 10% solution of potassium chromate, and a 0.73% solution of silver nitrate constitutes all the necessary equipment. For convenience the solutions may be housed in standard medicine bottles with one piece molded rubber caps (Fig. 1). The same size dropper should be used throughout. Five to 10 cc. of blood obtained from any convenient venipuncture site is allowed to clot in a test tube. To exactly 10 drops of serum obtained from this specimen a drop of the solution containing potassium chromate is added. A yellow-orange color is produced. The silver nitrate solution is now added, drop by drop, the number counted, until a reddish brown color is produced after the mixture is gently shaken. This end point is easily discernible. Each drop of silver nitrate solution required to produce this end point represents 15 mg. of chloride per 100 cc. of serum. The average normal patient will require between 23 drops* (equivalent to 345 mg. of chloride expressed as 575 mg. of sodium chloride per 100 cc.)

* Twenty-three drops represents 99 mEq. of chloride.

and 25 drops (equivalent to 375 mg. of chloride or expressed as 625 mg. of sodium chloride per 100 cc.). To check the results the procedure is repeated using 20 drops of serum. The value obtained should be exactly double.

Results. One hundred and twenty-seven determinations obtained from 42 patients were studied by this method. At the same time each specimen of blood was checked with the standard Schales and Schales mercurimetric method for determining serum chlorides[9]. Eighty-two specimens were obtained from 24 medical ward patients on a restricted salt diet and 45 specimens from 18 patients on a normal diet. In the majority of specimens there was close agreement in the two methods (Table I). There was a difference of less than 1% in 30 specimens (23.6%). In 53 specimens (41.7%) the difference was more than 1 and less than 5%, and in 32 specimens (25.2%) the difference was between 5 and 10%. There were 8 specimens (6.3%) with a difference of more than 10 and less than 15%. Four specimens (3.2%) demonstrated a difference of more than 15%.

Discussion. One of the striking features of the mercurial diuretics is the profuse excretion of urinary chlorides, and a lowering of the plasma chlorides[2,3,8,11]. Sodium is also lost in the urine, but since the body losses of sodium in the early stages of mercurial diuresis are isotonic with the serum, there is little fluctuation in the sodium concentration in the blood[7]. With prolonged mercurial diuresis hypochloremia characteristically develops. It is a well known clinical fact that when the plasma chlorides fall to a low level, 85 mEq. or less, the mercurial diuretics are ineffective, if not dangerous[1,12,16]. In the management of congestive heart failure it is important to recognize this refractory stage of

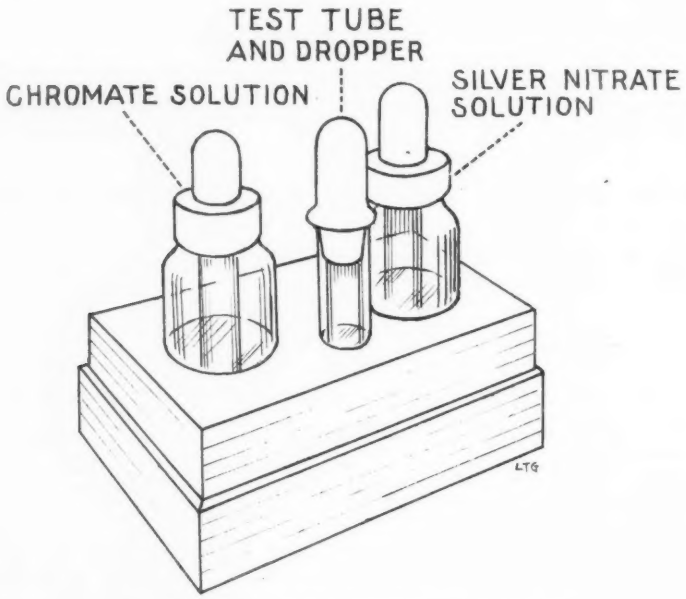

FIG. 1.—Kit for bedside determination of chloride.

hypochloremia since it can be corrected by the administration of ammonium chloride[1,16].

As a guide to mercurial diuresis, the pattern of urinary chloride excretion is easier to follow and a much more sensitive indicator of chloride depletion than the fluctuations of the chloride concentration in the blood. Along this line an interesting experiment was carried out by Van Slyke and Evans[17], who studied normal medical students artificially depleted of salt by means of gastric lavage. In this experiment, on the second day of continuous gastric suction, urinary chlorides promptly fell to zero, whereas, the plasma chloride showed only a decrease of 6% from the control levels. Significant changes were observed in the plasma chloride concentration only after the depletion period became profound. In suspecting chloride depletion, therefore, in patients receiving mercurial diuretics, undue reliance should not be placed on serum chloride determinations unless they are definitely low. The degree of hypochloremia sufficient to produce a refractory state to mercurial diuretics varies[16]. In some patients a refractory state is observed with low normal values. It should be emphasized that the so-called refractory heart failure developing in patients receiving mercurial diuretics is a complicated subject in which a host of factors may be responsible. Chloride depletion is merely one of these factors.

In patients receiving mercurial diuretics serum chloride determinations are often neglected. In hospitals where modern laboratory facilities are available the fluctuations of blood chloride values in patients receiving mercurial diuretics can be followed with ease. Unfortunately, aside from the expense, these facilities are not always available to the average practitioner. It is appreciated that the method proposed is not sufficiently accurate for precise determinations of serum chlorides. The method, however, has sufficient merit to enable the clinician to screen out states of severe hypochloremia. The technique is particularly applicable at home since no special equipment is required and the method takes only a few minutes to perform. Comparing our method with the standard Schales and Schales method[9] which requires filtration and colorimetric studies, in over 90% of 127 specimens of blood studied for chlorides there was less than 10% difference in the results. Incidentally, during the course of this investigation 3 patients, unsuspected clinically, were found to have a profound state of hypochlore-

TABLE 1.—ANALYSIS OF 127 SPECIMENS COMPARING THE MODIFIED FANTUS METHOD FOR ESTIMATING THE SERUM CHLORIDES WITH THE STANDARD SCHALES AND SCHALES METHOD[9]

Agreement in 2 methods	*Number of specimens from patients on a low salt diet*	*Specimens from patients on a normal diet*	*Total specimens*
0 to 1% variation	19	11	30 (23.6%)
1 to 5% variation	34	19	53 (41.7%)
5 to 10% variation	22	10	32 (25.2%)
10 to 15% variation	4	4	8 (6.3%)
above 15% variation	3	1	4 (3.2%)

mia. Following the administration of salt these patients demonstrated a striking improvement in their clinical course.

Summary. As a guide to mercurial diuresis a simple, inexpensive bedside method for examining serum chlorides is presented.

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ANTAGONISM AND ADDITION FROM COMBINATIONS OF AUREOMYCIN AND PENICILLIN IN THE TREATMENT OF PNEUMOCOCCIC INFECTIONS IN MICE

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During the past several years, as more antibiotics have become available, there has been renewed interest in the value of combining 2 or more of these agents in the treatment of certain recalcitrant infections. Laboratory studies which have been done *in vitro* by Jawetz and his associates on the effect of certain combinations of antibiotics have demonstrated an antagonistic effect of chloramphenicol, and to a lesser extent of aureomycin, terramycin or sulfonamides on the bactericidal power of penicillin against certain penicillin-sensitive bacteria[4,5,6]. In experimental infections of mice with Group A *Streptococcus pyogenes* and *Klebsiella pneumoniae* less adequate protection was observed when penicillin was combined with one of these agents than when an equal dose of penicillin was used alone[11]. In contrast, some bacterial strains have been shown to be killed more effectively *in vitro* by a combination of penicillin with aureomycin, terramycin or chloramphenicol[1,3,4,8,10].

In some clinical infections where treatment with a single drug has been unsatisfactory, the use of one of these combinations of antibiotics has been quite effective[2,7,12]. On the other hand, from the treatment of a series of patients with pneumococcic meningitis, there is evidence that aureomycin may have reduced the efficacy of penicillin therapy[9].

To delineate the factors which determine whether addition or antagonism might be expected to occur, when aureomycin and penicillin are used simultaneously, we have studied the treatment of pneumococcic infections in mice. The results of the experiments in which the antibiotics were given as a single dose are reported here. The results when multiple doses were given are reported in a succeeding paper.

Materials and Methods. The Cooper strain of Type I pneumococcus* was maintained in tryptosephosphate broth, pH 7.4 wih 2% sheep red blood cells. Prior to use, the organism was passed serially in mice until maximum virulence was obtained. The iden-

* Obtained from Dr. Howard J. Shaughnessy, Laboratory Division of the Illinois State Department of Public Health.

tity of the strain was established by specific Quellung reaction. Dilutions for animal inoculation were made in sterile 0.85% saline solution from an 18-hour blood-broth culture, and the infecting dose was determined by serial pour-plate counts.

Female white mice of the Harlan strain, weighing approximately 20 gm., were used throughout the study. The minimal lethal infecting dose for 100% of mice when injected by the intraperitoneal route was 10 to 100 organisms. The experimental infection for therapeutic trials was produced with 50 to 45,000 minimal lethal doses. An untreated group of animals was infected for each experiment to serve as a control on the virulence of the infection. Mouse deaths and survivors were counted daily for 5 days.

Aureomycin hydrochloride with sodium glycinate* was diluted with sterile saline solution for each experiment immediately prior to use. Crystalline sodium penicillin G was dissolved in saline solution, stored at −20° C. and individual tubes were thawed as used. Combinations of aureomycin and penicillin were administered (1) before infection and mixed before injection; (2) before infection, injected separately; (3) concurrently at 2 or 6 hours after infection; (4) aureomycin 4 hours before penicillin, given 2 and 6 or 6 and 10 hours, respectively, after infection and (5) penicillin 4 hours prior to aureomycin, 2 and 6 hours, respectively, after infection. An equal number of mice were given each antibiotic alone in the same dose and time interval as was used in the group receiving the combination of antibiotics. In most experiments 20 mice were used in each treatment group.

Results. The minimal inhibitory concentration of penicillin and aureomycin for the Cooper strain of Type I pneumococcus as determined *in vitro* was 0.0012 mcg. (0.002 units) per cc. of penicillin and 0.03 mcg. per cc. of aureomycin.

Eighty-two experiments have been performed upon infected mice in which a single dose of aureomycin and penicillin was administered. Among 452 infected and untreated mice, 93.5% died within 24 hours and none lived as long as 48 hours. A smaller number of mice which were not infected, received the largest doses of both drugs which were used and all of them lived.

The effect of increasing the dose of each agent on the probability of survival for 5 days is shown in Fig. 1. In the case of both agents, there is a direct correlation between dose and probability of survival in the 5 to 80% protective range. However, in the case of aureomycin the percentage of survivors increased as an arithmetic function of the dose, whereas a logarithmic increase in the dose of penicillin was required to produce a similar linear increase in the per cent of survivors.

When treatment with the 2 antibiotics was combined, 3 patterns of response were observed, as shown graphically in Fig. 2: 1) the protection afforded by penicillin was significantly decreased by combining it with aureomycin, that is, antagonism of penicillin resulted. Results of such an experiment are shown in the left hand panel. 2) Aureomycin had no effect on the number of survivors or the rate at which deaths occurred. This is apparent in the center panel. 3) Aureomycin plus penicillin decreased significantly the fatality rate as compared with an equal dose of penicillin alone. Thus addition resulted from a combination of the 2 antibiotics. This result is shown in the panel on the right.

The size of the infecting inoculum was not the factor responsible for determining whether antagonism or addition would result in response to treatment with penicillin and aureomycin combined. The effect of increasing the infecting inoculum from 6 to 6,000 minimal lethal doses is shown graphically in Fig. 3. Penicillin alone proved least effective when a large number of lethal doses were given. On the other hand, aureomycin was antag-

* Kindly supplied by the Lederle Laboratories Division, American Cyanamide Company, Pearl River, New York.

onistic to the protective effect of penicillin regardless of the size of the infecting inoculum although the magnitude of the difference between the results obtained with penicillin alone or combined with aureomycin varied.

In Table 1 are shown the results of 14 experiments in which a dose of aureomycin which gave very little protection alone was combined with a submaximally protective dose of penicillin. The difference between the effect of penicillin used alone and in combination with aureomycin is expressed as the percentage of mice which survived for 5 days. In the case of aureomyin, however, the doses administered were insufficient, usually to

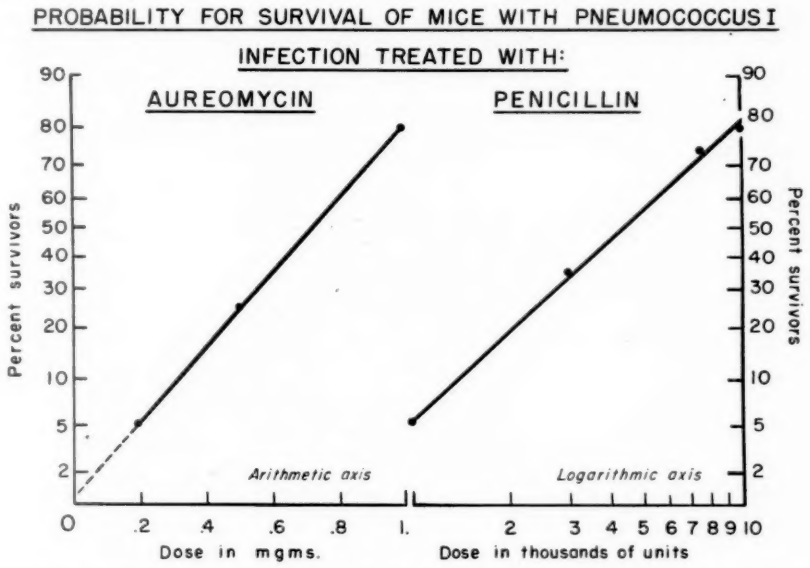

FIG. 1.—The Effect of Increasing the Dose of Aureomycin or Penicillin on the Probability For Survival of Mice Infected With Pneumococci

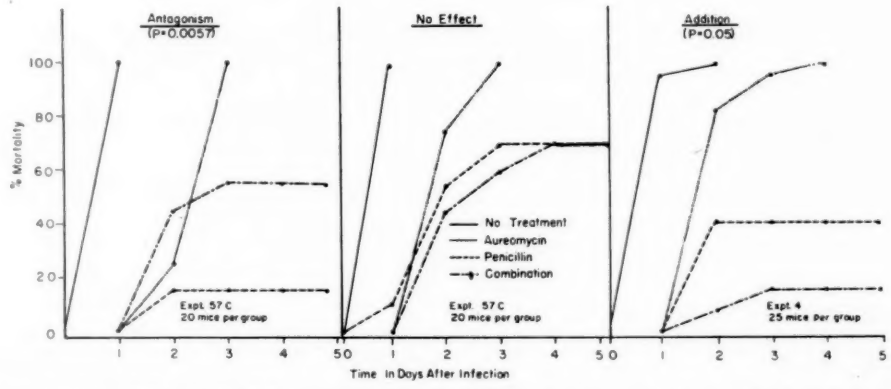

FIG. 2.—Varied Patterns of Response Obtained When Aureomycin Was Added to Penicillin in the Treatment of Pneumococcic Infections of Mice

produce survivors when it was given alone. Accordingly, the mean number of mouse survival days has been used in order to quantitate the effect obtained from aureomycin. In 6 experiments the protection from penicillin was antagonized by aureomycin, in 5 addition occurred when aureomycin was combined with penicillin, and in the remaining 3 experiments aureomycin had no influence upon penicillin activity. The differences were not statistically significant when all of the experiments were added together. When the individual experiments were analyzed statistically, however, the results were significant ($p = 0.05$ or less) in 4 of 6 experiments in which antagonism was demonstrated and in 4 of 5 experiments where an additive effect was demonstrated.

Thus 2 opposite phenomena, each of statistical importance, resulted from the combination of aureomycin and penicillin, and under the circumstances of these experiments each occurred at about the same order of frequency and magnitude. Antagonism occurred in experiments where penicillin alone produced a low, intermediate or high per cent of survivors, but the degree and statistical validity of the antagonism was greatest when penicillin was highly effective. In 5 experiments where aureomycin was additive when combined with penicillin, the protection afforded by penicillin alone was either zero or 60%. On the other hand, in 3 experiments where aureomycin had no effect upon penicillin activity the survival rate from penicillin alone was of the same order, that is zero to 60%. When aureomycin alone tended to afford the lowest protection, antagonism of penicillin activity was observed and when its effect was greatest the results with the combination were additive.

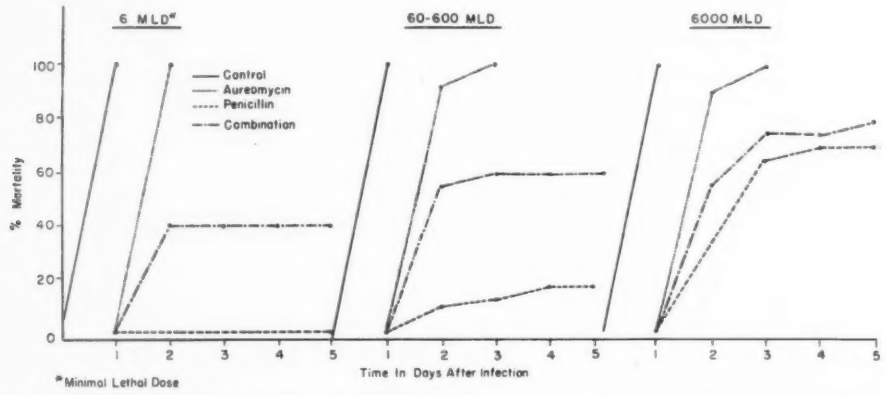

FIG. 3.—The Influence of the Size of the Infecting Inoculum Upon the Therapeutic Effect of Aureomycin and Penicillin Combined in the Treatment of Pneumococcic Infections in Mice

In 21 experiments treatment was delayed for 6 hours after the initiation of infection. The results of these experiments have been analyzed from data similar to that given in the preceding table and the summary is presented in Table 2. A combination of aureomycin and penicillin was less effective than penicillin alone in 11 experiments. In 4 of these the antagonism was statistically significant. Aureomycin and penicillin combined produced more survivors than the same dose of penicillin alone in 4 experiments but in

TABLE 1.—THE EFFECT OF CONCURRENT ADMINISTRATION OF AUREOMYCIN AND PENICILLIN BEFORE INFECTION UPON PER CENT SURVIVORS COMPARED WITH EACH AGENT GIVEN ALONE

	Number Mice Per Group	*M.S.D.† Aureomycin*	*% Survivors (5 Days)*		*Significance* P*
			Penicillin	*Combination*	
	A. Antagonistic Effect				
	(6 Experiments)				
	20	0.5	25	5	0.05
	20	1.0	30	10	0.10
	20	1.2	30	25	0.70
	6	1.65	67	20	0.05
	20	1.25	85	45	0.006
	20	1.2	85	45	0.006
Subtotal	106	1.13	51.9	25.5	
	B. Additive Effect				
	(5 Experiments)				
	20	1.25	0	15	0.05
	6	2.35	0	50	0.02
	25	1.2	60	84	0.05
	20	2.95 (30)	60	100	0.01
	5	3.0 (40)	60	100	0.07
Subtotal	76	2.15	36	69.8	
	C. No Effect				
	(3 Experiments)				
	20	1.2	0	0	
	20	1.25	30	30	
	10	1.8	60	60	
Subtotal	50	1.42	30	30	
TOTAL	232	1.50	43.9	38.8	

† M.S.D. = Mean Survival Days, controls = 0.09. When there were survivors for 5 days the per cent of mice surviving is shown in parentheses.

* Based on the Standard Error of the Difference between penicillin alone and penicillin plus aureomycin.

TABLE 2.—THE EFFECT OF A NONPROTECTIVE DOSE OF AUREOMYCIN AND A SUBMAXIMALLY PROTECTIVE DOSE OF PENICILLIN UPON THE PER CENT SURVIVORS WHEN ADMINISTERED CONCURRENTLY 6 HOURS AFTER INFECTION

Result	*Number of Experiments*	*M.S.D.† Aureomycin*		*% Survivors 5 Days*				*Number of Significant Experiments**
				Penicillin		*Combination*		
		Av.	*Range*	*Av.*	*Range*	*Av.*	*Range*	
Antagonistic	11	1.0	(0.6–1.45)	70.9	(35–95)	45.5	(0–90)	4
Additive	4	1.03	(0.25–1.4)	32.5	(0–65)	45	(5–85)	0
No Effect	6	1.59	(0.6–3.6)	33.3	(0–100)	33.3	(0–100)	0
TOTAL	21	1.16		49.1		39.2		

† M.S.D. = Mean Survival Days. Controls = 0.09. No survivors for 5 days.

* Individual experiments significant at the 5% level.

none of them was the difference statistically significant.

The occurrence and significance of antagonism was increased when the administration of aureomycin preceded that of penicillin and treatment was delayed until after the initiation of infection. Thus, in 47 experiments aureomycin was given 2 hours after infection and followed by penicillin 4 hours later (6 hours after infection). The results of these observations are summarized in Table 3. A lowering of the survival rate below that which occurred with penicillin alone, in other words, antagonism, was observed in 26 experiments, of which 14 were individually statistically significant. In 13 experiments the effect of combining both antibiotics was additive. Six of these were individually significant. In 8 instances there was no difference between penicillin alone and the combination of antibiotics. It is apparent that the average survival afforded by aureomycin alone was highest in the experiments where an additive effect was observed.

TABLE 3.—THE EFFECT OF TREATMENT WITH A COMBINATION OF AUREOMYCIN AND PENICILLIN UPON THE PER CENT SURVIVORS WHEN AUREOMYCIN WAS ADMINISTERED 4 HOURS BEFORE PENICILLIN, AND GIVEN 2 AND 6 HOURS AFTER INFECTION

Result	Number of Experiments	M.S.D.† Aureomycin		% Survivors 5 Days				Number Significant*
				Penicillin		Combination		
		Av.	Range	Av.	Range	Av.	Range	
Antagonistic	26	1.18	(0.05–2.4)	45.3	(5–100)	25.0	(0–80)	14
Additive	13	2.15	(0.05–4.8)	44.7	(0–86)	66.7	(5–100)	6
No Effect	8	0.72	(0–2.0)	31.3	(0–100)	31.3	(0–100)	0
TOTAL	47	1.38		42.5		37.4		

* Individual experiments significant at the 5% level.

† M.S.D. = Mean Survival Days. Control 0.09.

The relationship of the effectiveness of aureomycin or penicillin alone to whether antagonism or addition was observed, when the same doses were used in combination with the other antibiotic, is shown in Table 4. When the two drugs were administered concurrently, significant antagonism tended to decrease as the protection from aureomycin increased. In the case of penicillin, antagonism occurred most frequently with highly protective doses. When aureomycin preceded penicillin by 4 hours as shown on the right, the importance of the level of effectiveness of aureomycin alone in determining antagonism or addition in combination with penicillin was definite. The relationship of penicillin was less definite, but antagonism still occurred predominantly where penicillin gave the most protection when used alone.

If one constructs a ratio of the effectiveness of penicillin alone to that of aureomycin alone, based on the mean survival days, and correlates this with the occurrence of antagonism or addition, there is a rather clear delineation of the circumstances under which each phenomenon occurred. When concurrent administration of the antibiotics resulted in significant antagonism the ratio averaged 3.56 with a range of 2.21 to 4.66. When significant addition occurred the average ratio was 1.6 and ranged from 0.88 to 2.83. In experiments where aureomycin pre-

ceded penicillin by 4 hours, the corresponding ratios for antagonism and addition were 3.1 (1.77 to 4.30) and 0.64 (0.3 to 0.89) with 2 exceptions in which the effect of aureomycin alone differed insignificantly from the untreated animals.

Two experiments in which penicillin was given 4 hours before aureomycin showed no interference with penicillin activity even though the ratio was favorable for antagonism.

maximally protective dose of penicillin is compared with the same dose given 4 hours after an increasing amount of aureomycin. Under these circumstances the first effect of aureomycin was additive. The apparent mechanism by which addition resulted was the inhibition of the infecting inoculum during the time prior to administration of penicillin by a dose of aureomycin which was not great enough to interfere with penicillin activity when it was given

TABLE 4.—THE INFLUENCE OF PROTECTION FROM AUREOMYCIN OR PENICILLIN ALONE ON THE EFFECT OF A COMBINATION OF PENICILLIN PLUS AUREOMYCIN

Effect of a Single Antibiotic		*Effect of Combination of Aureomycin and Penicillin*					
		When Administered Concurrently			*When Aureomycin Was Administered 4 Hours Before Penicillin*		
% Survivors 5 Days	*M.S.D.†*	*Number of Experiments*	*Antagonism**	*Addition**	*Number of Experiments*	*Antagonism**	*Addition**
AUREOMYCIN							
0	0.5	3	–	–	13	–	2
0	0.5 –1.0	5	2	–	4	1	–
0	1.05–1.50	20	5	2	17	11	–
0–15	1.51–2.50	4	1	1	7	2	–
35–90	2.51–5.0	3	–	1	6	–	4
PENICILLIN							
0	0 –1.0	–	–	–	3	–	1
0–25	1.01–2.0	9	1	1	8	–	1
0–45	2.01–3.0	7	2	1	10	2	2
50–75	3.01–4.0	8	1	2	8	4	1
75–100	4.01–5.0	11	4	0	18	8	1

* Includes only the experiments which were statistically significant at the 5% level.
† M.S.D. = Mean Survival Days. Control 0.09.

Figure 4 summarizes the observed relationships of aureomycin and penicillin combinations. In the upper left hand panel the effect upon the per cent survivors of an increasing dose of penicillin is compared with the effect of the same dose administered 4 hours after a constant amount of aureomycin. Under these circumstances aureomycin was antagonistic throughout the entire range of penicillin dosage but most significantly so when penicillin alone was highly protective. In the panel immediately below, a constant sub-

4 hours before the penicillin. Increasing doses of aureomycin then caused antagonism of penicillin until the dose of aureomycin approached that which would produce an appreciable number of survivors when used alone. Beyond this dose, further increments exerted an additive influence upon penicillin.

In the panels on the right in Fig. 4, similar data are shown for aureomycin. Penicillin in any dose tended to increase the survivors above the per cent obtained from a poorly protective dose of aureomycin alone, as shown in the

lower panel, and a protective dose of penicillin increased the per cent survivors obtained with any dose of aureomycin, as noted in the upper panel on the right.

Discussion. The effect upon bacterial inhibition of combining 2 or more partially effective agents has been classified in the literature as antagonistic, indifferent, additive or synergistic and it has been shown that any particular combination of antibiotics may produce antagonism against one species of bacteria and synergism against a different species[8]. The present studies indicate, in addition, that a uniform experimental infection produced by the same bacterial strain also may result in antagonism or addition of antibiotic activity following treatment with penicillin and aureomycin combined.

Thus, the production of antagonism or addition is not necessarily a constant function of the particular antibiotics combined nor is it merely a characteristic of the specific bacterial infection being treated. Rather it is related to the potential effectiveness of each agent acting alone and the relationships of the effectiveness of the therapeutic agents to each other.

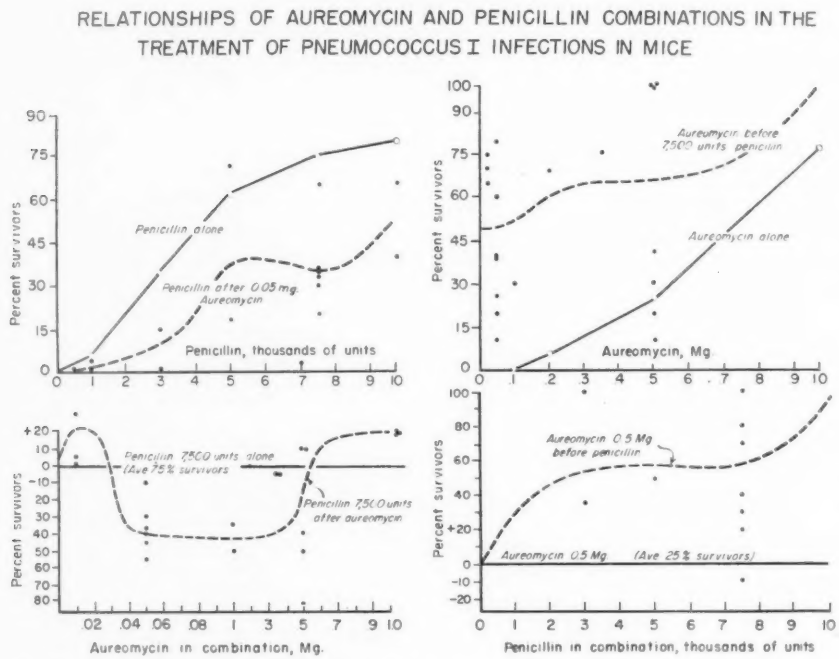
RELATIONSHIPS OF AUREOMYCIN AND PENICILLIN COMBINATIONS IN THE TREATMENT OF PNEUMOCOCCUS I INFECTIONS IN MICE
Percent survivors
Penicillin alone
Penicillin after 0.05 mg. Aureomycin
Penicillin, thousands of units
Penicillin 7,500 units alone (Ave 75% survivors)
Penicillin 7,500 units after aureomycin
Aureomycin in combination, Mg.
Aureomycin before 7,500 units penicillin
Aureomycin alone
Aureomycin, Mg.
Aureomycin 0.5 Mg before penicillin
Aureomycin 0.5 Mg. (Ave 25% survivors)
Penicillin in combination, thousands of units

FIG. 4.—The Relationships of the Effect of Aureomycin and Penicillin When Used in Combinations to the Effect of Each Antibiotic Used Independently in the Treatment of Pneumococcic Infections in Mice

From these studies the circumstances under which antagonism and addition are likely to occur can be defined as they concern pneumococcic infections in mice. Penicillin does not interfere with the protective effect of aureomycin but under certain conditions aureomycin interferes with the protective effect of penicillin. While such antagonism may be observed regardless of the degree of protection obtained from

penicillin alone its frequency and significance is greatest when penicillin is highly protective. Aureomycin must be relatively nonprotective to cause antagonism and its capacity to do so is greatest when administered prior to penicillin.

When the ratio of the protection from penicillin alone to that from aureomycin alone is high, conditions are favorable for antagonism. Conversely, when this ratio is of low order, the occurrence of significant addition from the use of the combined antibiotics is likely. The absolute numerical value of the ratio is inconsequential since it may be expected to vary under different conditions of infection and treatment and in different hosts.

In regard to the mechanism of action, this ratio does not appear to be an expression of a chemical or molecular relationship of one drug to the other, but rather, as stated above, it is primarily related to the level of effectiveness of one antibiotic to the effectiveness of the other.

We have not attempted to determine whether true synergism or merely simple addition occurred when the combination of penicillin and aureomycin showed protection which was superior to that obtained with penicillin alone. The reason for this is that the relationship of the protection afforded to the dose of the drug, the time it is administered and the size of the infecting inoculum is not of the same order for both agents. The probability for survival after treatment with aureomycin has an arithmetic relationship to the dose whereas the probability for survival after treatment with penicillin varies as the logarithm of the dose. Variations in the size of the infecting inoculum and delay in initiating treatment affect the response to penicillin to a much greater extent than they affect the response to aureomycin.

Neither does the presence or absence of statistical significance in the sum of the experiments performed have any importance. Thus the distribution of the total in Table 1 showed neither antagonism or addition of statistical significance while the total in Tables 2 and 3 indicated the occurrence of significant antagonism. Since 2 opposite phenomena are represented among the experiments the sum indicates only the balance in the frequency of occurrence of one of these phenomena against the other. When the conditions favorable for the occurrence of each can be defined as has been done from the material presented here, it becomes possible to predetermine the result. Unless such studies include experiments in all ranges of doses and dosage ratios the results may be statistically weighted. These circumstances might explain some apparently conflicting results reported in the literature.

In the light of this experience the results obtained in the treatment of the patients with pneumococcic meningitis might be explained by the relative effectiveness of the concentrations of each of the antibiotics obtained in the central nervous system with the respective doses which were used. Similarly, antagonism might be expected to occur from aureomycin and penicillin in the treatment of any infection in which an effective concentration of both agents, but in particular aureomycin, is not obtained at the site of infection by the doses used. On the other hand, addition might result from combined therapy when substantially effective concentrations of both antibiotics penetrate into the area of infection or when the etiologic organism is relatively resistant to penicillin alone. In these respects the present observations conform to the body of clinical experience on the results of combining aureomycin, or another agent which is principally bacteriostatic *in vitro*, with

penicillin, or an antibiotic which is principally bactericidal. In addition, they may have application as a basis for the logical utilization and restrictions of antibiotic combinations in clinical infections.

Summary. An induced infection of mice with Type I pneumococcus has been treated with combinations of aureomycin and penicillin administered as a single dose of each antibiotic. Eighty-two individual experiments were performed in which the per cent of mice surviving 5 days after treatment with a combination of penicillin and aureomycin was compared with the per cent of mice surviving after treatment with each of the drugs when administered alone. The results have been analyzed for the occurrence of significant differences in the survival rate among these therapeutic groups. Aureomycin was observed to have both an antagonistic and an additive effect upon the therapeutic activity of penicillin when a combination of both agents was used in treatment. The conditions favorable for the occurrence of each of these phenomena are defined in relation to the therapeutic effectiveness of each of the antibiotics when administered alone. The results appear to correlate some differences observed in other laboratory and clinical studies on the antibacterial effect of combining penicillin and aureomycin.

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THE VALUE OF DIHYDROSTREPTOMYCIN IN PRE-OPERATIVE PREPARATION OF THE GUT*

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When dihydrostreptomycin, the less toxic reduced form of streptomycin, was introduced, Merck prepared some of this drug in tablet form for convenient oral dosage, with the hope that it might be of use clinically. Consequently a study was undertaken using these tablets in an attempt to reduce the number of bacteria in the intestinal contents. In various previous studies using preoperative sulphonamides [7,14,17,20,21,22,23,29] and streptomycin [1,10,11,15,18,19,24,25,28,33,34,35] chief attention was paid to the coliform bacteria, the fecal streptococci and the anaerobic sporeformers. Little was done to follow the effects of the antibacterial agents on that important group of intestinal bacteria, the non-sporulating anaerobic bacilli which seem to be consistently present in large numbers. Therefore the general plan followed in this study, in considering the problem of intestinal antisepsis, was to watch the decrease and increase of both aerobic and anaerobic bacteria of the feces as therapy with the antibacterial agents proceeded.

As appropriate cases for the study of prophylactic treatment of the bowel presented themselves, the patients were given dihydrostreptomycin tablets by mouth, and fecal specimens were studied before, during and after treatment.

Material. The fecal flora of 14 patients in hospital were examined, and the results are presented here. Most of them had gastrointestinal disorders, but not all underwent surgical operations on the bowel.

The coliform and total viable bacterial counts, both aerobic and anaerobic, were carried out on the intestinal flora of patients whose diagnoses included: 6 carcinoma of the colon, 3 of which had had previous operations; 2 diverticulitis, both with previous colostomies; 4 colitis, one with previous colostomy. Two patients with no gastrointestinal disease were included. The patients were usually on a low-residue hospital diet; otherwise no attempt was made to modify the type of food or its quantity. Of the 14 cases, one was a normal control receiving no drugs; four received dihydrostreptomycin; 9 had sulfathaladine as well as dihydrostreptomycin. (The daily dose of sulfathaladine was 1 gm. every 4 hours.) One of the patients was started on dihydrostreptomycin, and given sulfathaladine on the fourth and fifth days; on the sixth day these two drugs were stopped, and terramycin was given alone for 2 days. Another of the dihydrostreptomycin patients, who had not received any therapy for 11 days, was also given terramycin alone for 2 days.

Method. The dihydrostreptomycin was removed as completely as possible by washing the specimen 3 times in sterile distilled water with high speed centrifugation. The small amount of drug which was found to be carried over would not be sufficient to inhibit the growth of the organisms. (The filter paper disc method of Loo *et al.*[16] was used to determine the fecal level of dihydrostreptomycin after the washings.) In a preliminary experiment, duplicate bacterial counts,

* This work was made possible by a grant from Merck and Co. Limited.

on washed and unwashed specimens from patients receiving no oral antibacterial agents, revealed no significant differences in numbers. The sulfathaladine was neutralized with a 5 mg./100 cc. aqueous para-amino-benzoic acid solution. The original 1:10 dilution was made in this, and allowed to stand for 5 minutes in the ice box before the serial 1:10 dilutions were made.

As each specimen was received, a small amount was weighed in a screw-capped sterile bottle, and sterile distilled water (or para-amino-benzoic acid solution) was added to give a 1:10 dilution, on the basis of 9 cc. of water per gram of stool. (If the patient was receiving dihydrostreptomycin, the stool was washed before this 1:10 dilution was made.) This bottle was thoroughly shaken mechanically to give a uniform suspension. From this suspension, a series of ten-fold dilutions was made in sterile distilled water so that the last tube was 10^{-12} times the concentration of the original stool specimen.

From each tube of this series, three 0.05 cc. samples were taken and distributed evenly with a platinum wire spreader over the surface of one MacConkey plate and two blood agar plates. The MacConkey plate and one blood agar plate were incubated aerobically and the other blood agar plate, anaerobically. The method used for obtaining anaerobic conditions was a modification of the McIntosh and Fildes anaerobic jar. All incubation was carried out at 37° C.

After 24 hours' incubation, the colonies on the MacConkey and aerobic blood plates were counted, and the total number of coliform-like organisms, and the total number of all organisms growing aerobically, recorded. After 48 hours, the plates were checked for the appearance of any new colonies. The total number of all organisms growing on the anaerobic blood agar plate was counted after 48, and checked after 96 hours incubation. From the counts of these 3 plates, the number of aerobic organisms, other than coliform-like varieties, and the number of anaerobic organisms could also be calculated. In addition, the approximate numbers of the different types of colonies present, both aerobic and anaerobic, were given.

The various organisms occurring in the feces were isolated and identified as accurately as possible using the classification in Bergey's Manual of Determinative Bacteriology[3]. The anaerobic bacteria presented a greater problem than did the aerobic species. Much confusion exists in the present classifications of the non-sporulating anaerobic bacilli, which are usually the organisms found in the feces in largest numbers[2,5,6,12,13,30,31,32]. For the most part, isolation of these anaerobic bacteria was only possible from the higher dilutions where overgrowth of other organisms did not occur.

Identification of the Gram-negative anaerobic species was attempted by using Bergey's[3] key to 23 different species, but this was found to be unsatisfactory. These species have not been studied systematically and it is impossible to determine how many of them actually represent distinct species. There is much irregularity in the biochemical data which have been reported, especially in regard to the sugar fermentation reactions, as such a variety of media and methods has been employed.

Several groups of workers[8,9,13,27] recognized two types of anaerobic Gram-negative rods and adopted the convention of placing pleomorphic strains in a *Bacteriodes funduliformis* group and non-pleomorphic strains in a *Bacteroides vulgatus* (or *fragilis*) group.

In this study, it was decided to make a primary division of these Gram-negative anaerobic bacilli on the basis of their morphology in Gram-stained smears. Strains were considered pleomorphic if they formed large bodies and filaments, as was described by Dienes and Smith[4], and were identified as *Bacteroides funduliformis*. The non-pleomorphic strains occasionally had small filaments and irregularly stained cells, but these were never abundant. This second type included a somewhat heterogeneous group of organisms, and the lack of correlation among the various characteristics made clear-cut subdivision difficult. The sugar reactions were so extremely varied that they were not included in our classification. Indol production, gelatin liquefaction and H_2S production were used to separate further the various non-pleomorphic Bacteroides we isolated.

In reference to the Gram-positive anaerobic bacilli, we followed Skerman's[26] key and assumed that all Gram-positive anaerobic non-sporing rods with no true branching were species of the genus *Lactobacillus*. Metabolic and fermentation reactions showed much variation. On the basis of morphology, they were divided into 3 sub-groups: (1) Long thin bacilli in chains or winding filaments; (2) Not markedly pleomorphic, rather short regular bacilli; (3) Pleomorphic forms with bulbous ends and the appearance of branching.

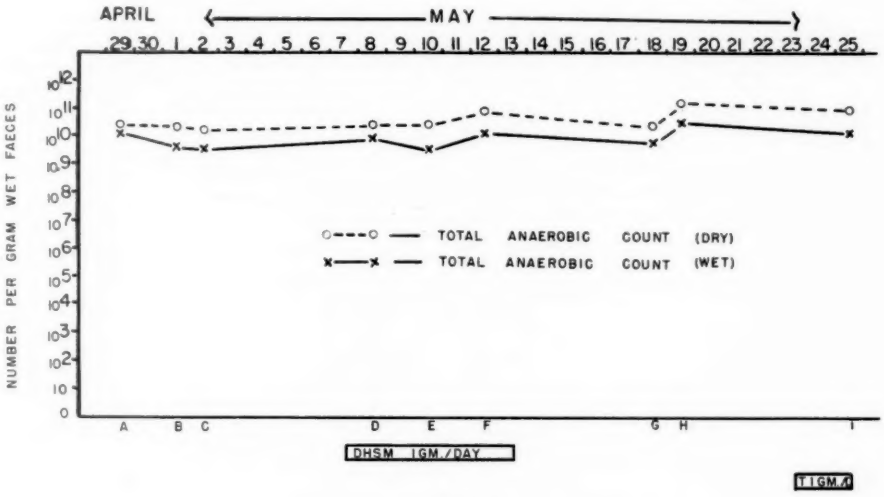
The antibacterial activity of dihydrostreptomycin was tested against all the various aerobic and anaerobic microorganisms which were isolated in the qualitative analysis of the feces before and during the course of oral administration of dihydrostreptomycin.

A series of halving dilutions of dihydrostreptomycin in peptone broth with an original concentration of 1024 mcg. per cc. was used to determine the sensitivity of each organism.

During the earlier stages of this study, it was noticed that the fluid content of the feces varied greatly. It was thought that a more accurate idea of the fluid content might be obtained by drying a sample of the stool to constant weight. Also, the effects on the counts by the antibacterial agents would be more accurately represented and easier to compare when referred to a constant dry weight of the specimen. Therefore, duplicate samples of each stool specimen were weighed out, one sample being for routine quantitative analysis and one being kept at approximately 100°C in a drying oven for 2 hours. Graph No. 1 illustrates that the curve is only straightened out slightly when the counts per gram of dry feces are plotted.

The factor for converting the number of organisms per gram of fresh wet feces into the number of organisms per gram of dry feces is the ratio between one gram of the fresh wet specimen to the weight of this amount when dried for 2 hours at 95 to 100°C.

Results. In reviewing the findings of the experimental work in this study, each patient will be discussed briefly. It would occupy too much space to give here detailed graphs and tables of all the cases. Therefore we will present only a few cases which illustrate pertinent points or typical effects of antibacterial agents upon the coliform, total aerobic, and total anaerobic counts.


APRIL
MAY
29 30 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
NUMBER PER GRAM WET FAECES
TOTAL ANAEROBIC COUNT (DRY)
TOTAL ANAEROBIC COUNT (WET)
A B C D E F G H I
DHSM 1GM./DAY
T 1GM./D

M.S. ♀ 31 CANCER OF SIGMOID

GRAPH 1

Factor for converting wet weight of feces to dry weight:

a = 2½	d = 4½	g = 5
b = 5	e = 5½	h = 4
c = 6	f = 6	i = 6½

The curves represent both strict and facultative anaerobes combined
DHSM = Dihydrostreptomycin
T = Terramycin

Case Reports. CASE 1. J. E., male, the one normal control who was studied, had never received previous treatment with streptomycin. This subject showed that changes in total numbers and kinds of bacteria do occur with-

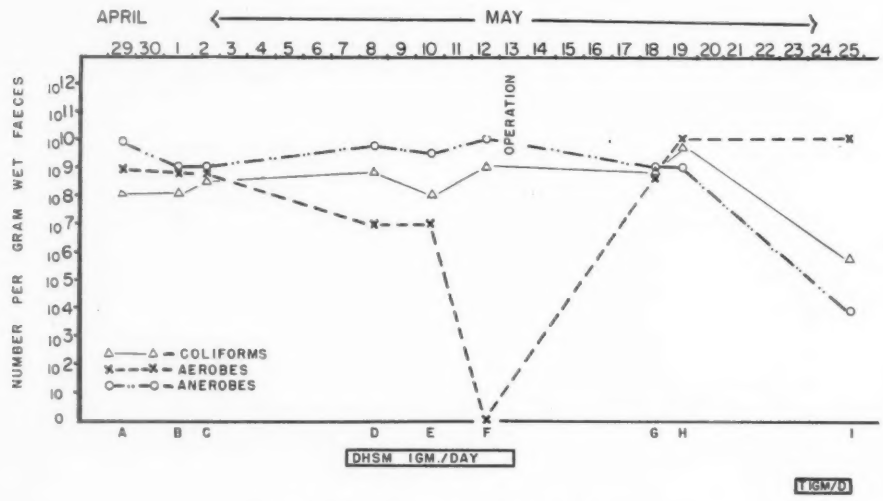
in certain limits in the normal feces when no oral antibacterial agents are being administered. The anaerobic bacilli isolated were found to be relatively resistant to dihydrostreptomycin, while the coliform group was less sensitive than was expected.

CASE 2. H.S., male, aged 48, had diverticulitis of the colon treated by a left hemicolectomy, with a transverse colostomy, and later closed by anastomosis to the sigmoid colon.

He was given 1 gm. of dihydrostreptomycin daily for 6 days.

She received 1 gm. of dihydrostreptomycin daily for 6 days pre-operatively, and 10 days after the abdomino-perineal resection, 1 gm. of terramycin daily for 2 days.

Oral dihydrostreptomycin did not cause any significant reduction in numbers of the coliform flora, although a simplification of kinds present did occur. The other aerobic species were reduced in numbers after 5 days of


APRIL
MAY
29 30 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
NUMBER PER GRAM WET FAECES
OPERATION
COLIFORMS
AEROBES
ANEROBES
A B C D E F G H I
DHSM 1GM./DAY
T 1GM/D

M.S. ♀ 31 CANCER OF SIGMOID

GRAPH 2

Effect of Dihydrostreptomycin on Fecal Flora in Case 3.
DHSM = Dihydrostreptomycin
T = Terramycin

CASE 6.—W. L. ♀ 51 ULCERATIVE COLITIS

Oral dihydrostreptomycin reduced the number of coliform and other aerobes, but the anaerobic flora showed little over-all reduction, although there were fewer different species isolated. It cannot be considered to have had much value in this case.

CASE 3. M.S., female, aged 31, had acute peritonitis of 4 days' duration resulting from a perforation due to carcinoma of the sigmoid colon. The peritoneal cavity was drained, and later an abdomino-perineal resection was done.

oral dosage. The total count of anaerobic organisms did not show any significant variation in the numbers or kinds present.

Terramycin greatly reduced both the numbers of coliform and anaerobic species, although large numbers of terramycin-resistant *Staphylococcus pyogenes* and micrococci persisted.

Graph 2 and Table 1 show the fluctuation in individual counts, while the total count of all organisms did not vary to any extent.

CASE 4. L. L., male, aged 40, had ulcerative colitis. He was given 1 gm. of dihydrostreptomycin daily for 2 days.

The oral dihydrostreptomycin did not cause any reduction in the fecal flora in this patient.

CASE 5. H.N., male, aged 23, had an appendectomy for recurrent appendicitis. This case was used as a control.

He was given 2 gm. of dihydrostreptomycin daily for 3 days.

She received dihydrostreptomycin 2 gm. daily for 5 days. Sulfathaladine on the fourth and fifth days. Terramycin 4 gm. daily for 2 days after the other two drugs were discontinued.

Oral dihydrostreptomycin caused a simplification of the coliform-like flora but this was accompanied by an increase in total numbers. The addition of oral sulfathaladine caused a decrease in the coliform count to the same level as in the pretreatment specimens. The other aerobic species were reduced in number after 2 days of oral dihydrostreptomycin, but had risen again to the original level after 4 days of dihydrostreptomycin and one day of sulfathaladine. The total count of the anaerobic organisms did not show any significant variations.

Terramycin eliminated both coliform-like organisms and anaerobic bacteria after 2 days. Enterococci and a species of yeast-like fungus persisted

TABLE 1.—CASE 3 (PATIENT M. S.) EFFECT OF ORAL DIHYDROSTREPTOMYCIN MAY 7 TO MAY 13

Specimen No. and date (description)	*Numbers/gram of wet feces*				
	Total aerobic	*Total anaerobic*	*Coliform*	*Aerobes other than coliform*	*Strict anaerobes*
a—Apr. 29 (formed)	1.5×10^9	1.5×10^{10}	4.5×10^8	1×10^9	1.5×10^{10}
b—May 1 (semi-formed)	2.5×10^9	6×10^9	3×10^8	2×10^9	3.5×10^9
c—May 2 (semi-fluid)	3.5×10^9	4.5×10^9	9×10^8	2.5×10^9	1×10^9
d—May 8 (semi-formed)	8.5×10^8	9.5×10^9	8×10^8	4×10^7	8.5×10^9
e—May 10 (semi-formed)	3×10^8	7×10^9	3×10^8	2.5×10^7	7×10^9
f—May 12 (semi-formed)	1.5×10^9	1.5×10^{10}	1.5×10^9	none isolated	1.5×10^{10}
g—May 18 (semi-formed)	5.5×10^9	8×10^9	4×10^9	1.5×10^9	2.5×10^9
h—May 19 (semi-formed)	5×10^{10}	5.5×10^{10}	2.5×10^{10}	2.5×10^{10}	4×10^9
ORAL TERRAMYCIN—MAY 23 TO MAY 25					
i—May 25 (semi-formed)	1.5×10^{10}	1.5×10^{10}	8.5×10^5	1.5×10^{10}	4×10^4

Oral dihydrostreptomycin did not cause any significant reduction in the coliform or anaerobic flora, but produced some simplification. The aerobic flora, other than coliforms, while undetected in the pretreatment specimen, increased to a higher level than that of either the coliform or anaerobic flora. The dihydrostreptomycin had no beneficial effect in this case.

CASE 6. W.L., female, aged 51, suffering from ulcerative colitis, was in hospital for investigation and medical therapy.

TABLE 2.—CASE 6 (PATIENT W. L.) EFFECT OF ORAL DIHYDROSTREPTOMYCIN: JUNE 3 TO JUNE 8

Specimen No. and date (description)	*Number/gram of wet feces*				
	Total aerobic	*Total anaerobic*	*Coliform*	*Aerobes other than coliform*	*Strict anaerobes*
a—May 31 (fluid-mucus)	4.5×10^6	3×10^9	2×10^5	4×10^6	3×10^9
b—June 2 (semi-fluid)	4.5×10^6	7.5×10^9	4×10^5	4×10^6	7.5×10^9
c—June 3 (semi-formed)	3×10^7	1.5×10^{10}	6×10^6	2.5×10^7	1.5×10^{10}
d—June 5 (semi-formed)	4.5×10^9	1.5×10^{10}	4.5×10^9	none isolated	8.5×10^9
e—June 6 (semi-formed)	1.5×10^9	2.5×10^{10}	1.5×10^9	none isolated	2.5×10^{10}
JUNE 6 TO JUNE 8, ORAL SULFATHALADINE WAS ALSO RECEIVED					
f—June 7 (semi-formed)	4.5×10^8	6×10^{10}	4.5×10^8	1.5×10^6	$6. \times 10^{10}$
g—June 8 (semi-formed)	1.5×10^7	6.5×10^7	4×10^5	1.5×10^7	5×10^7
ORAL TERRAMYCIN—JUNE 8 TO JUNE 10					
h—June 9 (semi-formed)	5×10^6	5×10^6	2×10^5	5×10^6	none isolated
i—June 10 (semi-formed)	1.5×10^7	1.5×10^7	less than 2×10^2	1.5×10^7	none isolated

TABLE 3.—CASE 3 (PATIENT W. L.) EFFECT OF ORAL DIHYDROSTREPTOMYCIN (JUNE 3 TO JUNE 8), ORAL SULFATHALADINE (JUNE 6 TO JUNE 8), AND ORAL TERRAMYCIN (JUNE 8 TO JUNE 10)

Organisms Isolated	*Approximate Nos/Gm. Feces*								
	(a) 31/5	*(= + 2/6*	*(c) 3/6*	*(d) 5/6*	*(e) 6/6*	*(f) 7/6*	*(g) 8/6*	*(h) 9 6*	*(i) 10/6*
AEROBIC									
E. coli grunthali	10^5	10^5	10^6	—	—	—	—	—	—
E. coli commune	10^4	10^5	10^6	—	—	—	—	—	—
E. coli neapolitana	10^4	—	—	—	—	—	—	—	—
A. aerogenes	10^3	—	10^6	10^9	10^9	10^8	10^5	10^3	—
Paracol. intermedium	10^2	—	10^4	—	—	—	—	—	—
Non-hemolytic enterococci	10^5	10^6	10^7	—	—	10^6	10^7	10^6	10^5
Hemolytic enterococci	—	—	10^5	—	—	—	—	—	—
Staph. pyogenes	10^6	10^3	—	—	—	—	—	—	—
Yeast-like fungus	—	—	—	—	—	—	10^3	10^4	10^7
ANAEROBIC									
Lactobacillus sp. II.	10^7	10^7	10^9	10^8	10^8	10^{10}	10^6	—	—
Bacteroides sp. A	—	10^8	10^8	—	10^{10}	10^8	—	—	—
" " *C*	10^9	10^9	10^9	10^8	—	—	—	—	—
" " *E*	10^8	—	—	10^8	—	10^{10}	10^6	—	—
B. funduliformis	10^9	10^9	10^{10}	10^9	10^{10}	10^{10}	10^7	—	—
B. melaninogenicus	10^3	10^4	10^4	—	—	—	—	—	—
Cl. perfringens	10^4	10^4	10^2	10^5	10^4	—	—	—	—
Str. foetidus	10^5	10^6	10^7	10^6	10^4	—	—	—	—
Str. lanceolatus	—	—	—	—	—	10^7	—	—	—

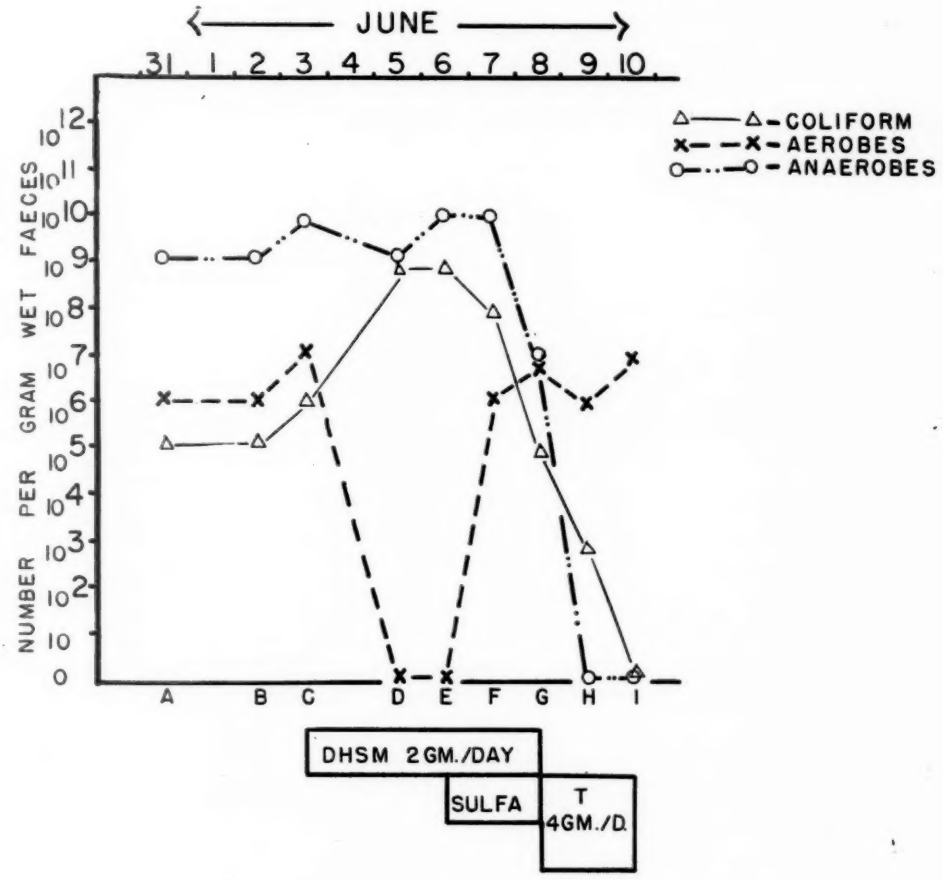
in large numbers, despite the large dose of terramycin used.

This illustrates in one case the effect of dihydrostreptomycin alone and in combination with sulfathaladine, and later the substitution of terramycin for these. The interesting effects on the fecal flora are shown in Tables 2 and 3 and Graph 3.

Case 7. J.E., male, aged 51, had diverticulitis of the sigmoid colon with peri-sigmoid abscess and perforation, treated by drainage of the abscess and a defunctioning transverse colostomy.

He was given sulfathaladine daily for 17 days, and dihydrostreptomycin 2 gm. daily from the third to the 15th day.

The coliform, aerobic and anaerobic counts all increased in number as the

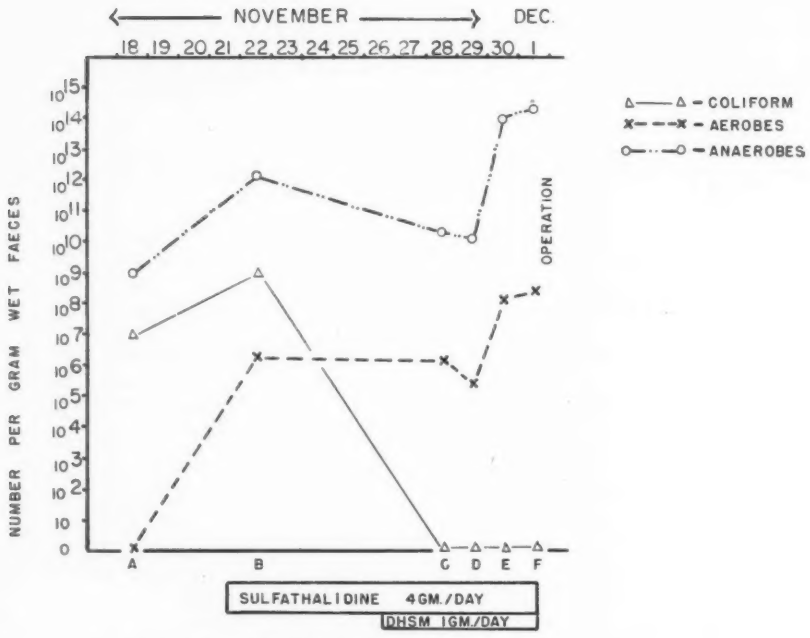


W.L. ♀ 51 ULCERATIVE COLITIS

GRAPH 3

DHSM = Dihydrostreptomycin
SULFA = Sulfathalidine
T = Terramycin

Case 10.—G. V. ♀ 52 CANCER OF SIGMOID



GRAPH 4

DHSM = Dihydrostreptomycin

TABLE 4.—CASE 10 (PATIENT G. V.) EFFECT OF ORAL DIHYDROSTREPTOMYCIN (NOV. 26 TO DEC. 1) AND ORAL SULFATHALADINE (NOV. 21 TO DEC. 1)

	Number/gram of wet feces				
Specimen No. and date (description)	*Total aerobic*	*Total anaerobic*	*Coliform*	*Aerobes other than coliform*	*Strict anaerobes*
a—Nov. 18 (dry-formed)	1×10^7	1.5×10^9	1×10^7	none isolated	1.5×10^9
b—Nov. 22 (dry-formed)	9×10^8	2×10^{12}	9×10^8	3×10^6	2×10^{12}
c—Nov. 28 (semi-formed)	2×10^6	3×10^{10}	less than 2×10^2	2×10^6	3×10^{10}
d—Nov. 29 (dry-formed)	6×10^5	1.5×10^{10}	less than 2×10^2	6×10^5	1.5×10^{10}
e—Nov. 30 (semi-formed)	2.5×10^8	1×10^{14}	less than 2×10^2	2.5×10^8	1×10^{14}
f—Dec. 1 (semi-formed)	4.5×10^8	3×10^{14}	less than 2×10^2	4.5×10^8	3×10^{14}

prolonged dosage of the two drugs continued. The antibacterial agents in this case were of no benefit, and were continued for too long a time.

CASE 8. S.B., male, aged 58, had carcinoma of the hepatic flexure treated by right hemicolectomy.

He received sulfathaladine for 3 days and dihydrostreptomycin, 1 gm. daily for 3 days, simultaneously.

She was given sulfathaladine for 6 days, and dihydrostreptomycin 1 gm. daily for the first 3 days of the sulfa therapy. On second admission she received sulfathaladine for 6 days and dihydrostreptomycin, 1 gm. on the fifth and sixth days.

The combination of sulfathaladine and dihydrostreptomycin for one day caused a reduction in the coliform count of from 10^7 to 10^3, and in the

TABLE 5.—CASE 10 (PATIENT G. V.) EFFECT OF ORAL DIHYDROSTREPTOMYCIN (NOV. 26 TO DEC. 1) AND ORAL SULFATHALADINE (NOV. 21 TO DEC. 1)

	Approximate Nos/Gm. Feces					
Organisms Isolated	(*a*) *18/11*	(*b*) *22/11*	(*c*) *28/11*	(*d*) *29/11*	(*e*) *30 11*	(*f*) *1/12*
AEROBIC						
E. coli communior	10^7	10^8	—	—	—	—
E. freundii	10^5	10^8	—	—	—	—
Achromobacter	—	10^8	—	—	—	—
Staph. pyogenes	—	—	10^6	10^5	10^3	—
Enterococci	—	—	10^5	10^5	10^8	10^8
Gram-positive rods*	—	10^6	10^5	10^2	—	10^2
Micrococci	—	—	10^4	10^2	10^2	10^2
Aer. spore-former	—	10^2	10^2	10^2	10^2	10^2
ANAEROBIC						
Lactobacillus sp. I	10^8	10^{11}	—	—	10^{14}	10^{13}
" " *II*	—	—	10^9	10^{10}	—	—
" " *III*	—	10^9	—	—	—	10^8
Bacteroides sp. A	—	—	10^{10}	—	—	10^{13}
" " *C*	10^8	—	—	—	—	—
" " *E*	—	—	10^{10}	10^9	10^{14}	—
" " *F*	—	—	—	—	—	10^{14}
" " *G*	10^9	10^{11}	—	—	—	—
B. funduliformis	—	10^{11}	—	—	—	—
B. melaninogenicus	—	10^4	—	—	—	—
Cl. perfringens	10^4	10^6	—	—	10^6	—
Cl. sporogenes	—	—	10^5	10^3	—	—
Str. foetidus	10^4	—	—	—	—	—
Str. lanceolatus	—	10^{11}	—	10^9	—	—
Str. intermedius	—	—	10^9	—	—	10^{13}

* Gram-positive aerobic, non-sporing rods; not identified.

The combination of sulfathaladine and dihydrostreptomycin caused reduction in the coliform count from 10^{13} to 10^7, while the other aerobic organisms showed a corresponding increase in numbers. Little effect was seen on the anaerobic organisms, and there was no change in the total anaerobic and aerobic counts.

CASE 9. A.B., female, aged 65, had carcinoma of the recto-sigmoid treated by anterior resection.

anaerobic count of from 10^{10} to 10^8, while the aerobes other than coliform showed a slight increase. A subsequent course of antibiotics 3 weeks after the operation showed no appreciable effect upon the bacterial counts, and an increased resistance to dihydrostreptomycin was noted in the organisms isolated.

CASE 10. G. V., female, aged 52, had an inoperable carcinoma of the sigmoid, for

which a palliative transverse colostomy was done.

She received sulfathaladine 4 gm. a day for 10 days, and dihydrostreptomycin 1 gm. daily from the 6th to the 10th day.

The combined use of sulfathaladine and dihydrostreptomycin caused a drop in the total coliform count to less than 200 per gram, while the aerobic organisms showed an increase in numbers and types. The effect on the total count of anaerobic flora was quite irregular. The individual species of anaerobes were reduced in numbers or eliminated, but other types appeared to take their places. The over-all effect of this extended oral administration of antibacterial agents was an increase in the total numbers of organisms present.

The graph (No. 4) for this case is presented because it illustrates an effect which is frequently seen when oral sulfonamides and dihydrostreptomycin in combination are administered. Tables 4 and 5 also illustrate this case.

CASE 11. L.M., female, aged 56, had carcinoma of the sigmoid with metastases, for which a palliative resection was done.

She received sulfathaladine for 16 days, and dihydrostreptomycin, 1 gm. daily, starting on the second day for 15 days.

The combined use of sulfathaladine for 3 days and dihydrostreptomycin for 2 days had eliminated the coliform-like organisms from the feces. After 2 weeks of oral dosage, the coliform count returned to the original level. No significant variations occurred in the total numbers of aerobic organisms other than coliform. The total numbers of anaerobic organisms showed an over-all decrease from 10^{16} to 10^{9}. In this case there was a reduction in the total number of organisms present, but large numbers of resistant coliform-like organisms developed.

CASE 12. L.R., female, aged 60, had carcinoma of the cervix uteri followed by radium proctitis which necessitated a defunctioning sigmoid colostomy.

She was given sulfathaladine for 4 days and dihydrostreptomycin, 2 gm. daily for 4 days, simultaneously.

The combined use of oral sulfathaladine and oral dihydrostreptomycin for 3 days temporarily suppressed the coliform organisms. The anaerobic count showed little change. The aerobic organisms other than coliform showed a 10-fold increase after 3 days and a 1000-fold increase after 4 days. No reversion occurred in the coliform count in this patient even after 4 days of the combined drug therapy, but large numbers of other aerobic and of anaerobic organisms appeared.

CASE 13. A.L., male, aged 24, had chronic colitis (or tuberculosis intestinalis) and a prolapsed transverse colostomy with an abscess to the exterior. A hemicolectomy was done.

He received sulfathaladine for 9 days and dihydrostreptomycin, 1 gm. daily for 9 days simultaneously.

The combined use of sulfathaladine and dihydrostreptomycin for 2 days, caused a drop from 10^{7} to 10^{4} in the coliform count, from 10^{8} to 10^{6} in the count of other aerobes, and from 10^{9} to 10^{2} in the anaerobic count. Further dosage caused a reversion in the counts due to the development of resistant forms. After 8 days of combined dosage there was an increase to 10^{9} in the coliform count, to 10^{11} in the count of aerobes other than coliform, and to 10^{6} in the anaerobic count. Both the coliform and other aerobes had counts higher than those of the pretreatment specimens.

The combination of sulfathaladine and dihydrostreptomycin in this patient was of no benefit in permanently reducing the bacterial counts and produced a highly resistant flora which was present at the time of the operation.

CASE 14. H.L., female, aged 60, had adenocarcinoma of the sigmoid colon, treated by abdomino-perineal resection.

She was given sulfathaladine daily for 6 days and dihydrostreptomycin, 2 gm. a day on the 4th, 5th, and 6th days.

The combined use of sulfathaladine for 5 days and dihydrostreptomycin for 2 days produced a drop from 10^8 to 10^4 in the total coliform count, the other aerobic organisms decreased from 10^6 to 10^4, and the total count of anaerobic flora dropped from 10^{10} to 10^5. In this case the combined dosage was effective in reducing the number of bacteria present to some extent, and was not given for a period long enough to produce reversions in count due to the development of a resistant flora.

Conclusions. These cases show that oral dihydrostreptomycin is far from being a satisfactory alimentary antiseptic. Our conclusions may be summarized as follows:

1. The oral administration of dihydrostreptomycin, either alone or in combination with sulfathaladine had an irregular and temporary effect upon the coliform, aerobic and anaerobic counts.

2. Only the coliform bacteria were affected consistently, and even this group built up early resistance to the drug.

3. The other aerobic organisms were irregularly affected, and on the whole it was noted that as one species of sensitive bacteria was suppressed, another species, resistant to dihydrostreptomycin, developed and kept the total count equal to or higher than the pretreatment levels. In this series, Proteus and Pseudomonas were not prominent.

4. There was little over-all effect upon the anaerobic counts.

5. Very few cases showed a decided reduction in the total number of organisms present, although, quite often, a simplification of the number of species present occurred.

6. After several days of oral dihydrostreptomycin, the total number of organisms present per gram in a sample of feces was often noted to be higher than the total number present in the pretreatment specimen.

7. Dihydrostreptomycin in tablet form cannot be considered a satisfactory intestinal antiseptic. It has no advantages over streptomycin and is less effective against some organisms.

8. Terramycin was used briefly as an intestinal antiseptic in 2 cases but further clinical experience is needed.

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THE USE OF CHLOROMYCETIN IN THE TREATMENT OF SALMONELLA CARRIERS IN A STATE INSTITUTION

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OUTBREAKS of Salmonella infections have always been a problem in state institutions. In our hospital, it has been routine for the past several years to obtain stool samples for bacteriologic analysis upon admission of each patient. In August, 1952, the number of reports positive for Salmonella infections suddenly increased greatly in number. At this time, however, there were no active cases and thus we considered those positive to be chronic carriers.

While plans were being discussed as to the proper treatment of such individuals, a number of active cases appeared, and therefore, it was decided to treat both the active cases and the carriers, inasmuch as the source of the active infections probably was the chronic carriers, although the possibility of contaminated foods, such as dried milk powder and powdered eggs which were used in the preparation of certain items in the diet, were also considered.

Although there is no specific therapy for salmonellosis, previous reports on the use of Chloromycetin were so encouraging as to arouse our interest in using this antibiotic for treating both the active cases and the chronic carriers. This report, however, concerns only the treatment of the carriers.

Materials and Methods. Patients in the various groups were selected on the basis of consecutive admissions demonstrating positive stool cultures. Upon determining the presence of Salmonella infection, the individuals were isolated in private rooms or wards. In all cases, strict isolation technique was carried out. Organisms isolated from these individuals were typed for species and were checked for sensitivity to Chloromycetin. In addition, samples of powdered milk and eggs were examined for the presence of contamination and found to be negative for Salmonella. Likewise, all employee and patient food handlers were re-examined. Contamination was limited to patient food handlers and those found positive were added to the groups to be treated. All patients were maintained on a regular diet supplemented with multivitamins and vitamin B complex. Blood examination and urine analysis were done on each patient prior to, during, and for several weeks following Chloromycetin therapy. In all except 2 patients who refused to cooperate, oral medication was used. The latter 2 were given the drug by the intravenous route once daily, and by the intramuscular route 3 times daily.

Results. The specific types of organisms isolated, and the frequency of occurrence of each, are summarized in Table 1. All organisms isolated were sensitive to Chloromycetin in a concentration of 1.56 to 3.12 mcg. per cc.

GROUP 1. Individuals in this group received 50 mg./Kg./24 hrs. for 5 days. Of 6 cases, only 3 were bacteriologically cured and met requirements for release from isolation. One of the above cases not responding was retreated with 75 mg./Kg./24 hrs. for 5 days and 50 mg./Kg./24 hrs. for 2 days. The

re-treatment with this higher dosage for a longer period of time proved successful.

TABLE 1.—FREQUENCY OF VARIOUS SALMONELLA TYPES

Species	Frequency
S. *montevidea*	5
S. *oranienburg*	4
S. *tennessee*	2
S. *newington*	1
S. *meleagridis*	2
S. *muenchen*	1
S. *tennessee* S. *oranienburg*	1
S. *montevideo* S. *manhatten*	1
S. *oranienburg* S. *montevideo*	2
S. *tennessee* S. *montevideo* S. *derby*	2
S. *tennessee* S. *oranienburg* S. *meleagridis*	1
S. *cholerae suis* S. *tennessee* S. *montevideo* S. *oranienburg*	1
S. *typhimurium* S. *montevideo* S. *cubana* S. *tennessee* S. *oranienburg*	1
Type unknown	1

GROUP 2. This group of 11 male patients was given 100 mg./Kg./24 hrs. for 7 days. Treatment was successful in 10 of the 11.

GROUP 3. Three of this group of 5 female patients were given 100 mg./Kg./24 hrs. for 7 days by the oral route, and the remaining 2 received 0.5 gm. intravenously once daily and 0.5 gm. intramuscularly 3 times daily for 7 days. Treatment was successful in 2 of the 3 given oral treatments, and both of those given parenteral medication responded satisfactorily. The patient not responding in this group had originally been in Group 1, so that this represented a second unsuccessful attempt.

GROUP 4. This group of 6 patients, which included the one unsuccessfully treated in Group 2 was given 100 mg./Kg./24 hrs. for 7 days. Five of the 6 patients were successfully treated and the sixth patient who remained positive was re-treated 2 weeks later with a successful result.

Throughout the entire course of the investigation, and for several weeks following, the blood and urine remained normal. A summary of a typical case from each group is shown in Table 2.

Discussion. Although a control group, who were treated only by the isolation and hygienic form of therapy was not included in this study, we believe from past experience with Salmonella infections in our Institution, that Chloromycetin was definitely a valuable adjunct. Since the institution of the regimen of treating all Salmonella carriers upon admission to the hospital, there have been no active cases.

The rather high dosage of 100 mg./Kg./24 hrs. for 7 days, which in our opinion represents the optimum schedule, may at first appear to be unduly high. However, when one considers that Chloromycetin is very rapidly absorbed from the small intestine, it can readily be seen that rather high dosage may be required in order to obtain a relatively high concentration in the lower bowel. The use of such high dosage however, resulted in no untoward effects in any of the patients studied. There was no nausea, vomiting, neurological, hepatic or renal disease observed during this study. It is also of interest to note, that this high dosage, even though repeated in some of the cases, produced no adverse effects on the hemopoietic sys-

TABLE 2

TYPICAL CASE	Salmonella Type	Chloromycetin Therapy - Dose -	Complete Blood Counts: Pre-Treatment*	One Week Post-Treatment*	Three Weeks Post-Treatment*	Groups 1 and 2, 12 Weeks Groups 3 and 4, 4 Weeks Post-Treatment*	Group 1 and 2, 6 Months Group 3, 3 Months Group 4, 2 Months Post-Treatment*	Post Treatment Feces (by weeks)
CASE NO. 1 FROM GROUP ONE	Typhi Murium Montevideo Cubana Tennessee Oranienburg	50 mg/Kg/day 4 equal doses q 6 hrs. x 5 days. 9 weeks later 100 mg/Kg/day x 7 days.	RBC: 4,700,000 WBC: 9,900 Hb. 18.9 g 1. 5. 2. Not 6. Not 3. Done 7. Done 4. 8.	RBC 4,930,000 WBC: 12,400 Hb. 18.6 g 1. 1 5. 3 2. 2 6. 68 3. 0 7. 23 4. 1 8. 2	RBC: 4,350,000 WBC: 12,000 Hb. 18.3 g 1. 0 5. 1 2. 0 6. 64 3. 0 7. 29 4. 0 8. 6	RBC: 6,100,000 WBC: 7,250 Hb. 15.8 g 1. 0 5. 4 2. 1 6. 53 3. 0 7. 38 4. 1 8. 0	RBC: 5,590,000 WBC: 8,000 Hb. 15.3 g 1. 0 5. 0 2. 3 6. 55 3. 0 7. 41 4. 0 8. 1	1. Negative 2. Negative 3. Negative After Second Series
CASE NO. 2 FROM GROUP TWO	Tennessee Montevideo Derby	100 mg/Kg/day 4 equal doses q 6 hours x 7 days.	RBC: 6,350,000 WBC: 7,500 Hb. 18.6 g 1. 5. 2. Not 6. Not 3. Done 7. Done 4. 8.	RBC: 5,700,000 WBC: 8,750 Hb. 18.6 g 1. 0 5. 1 2. 2 6. 73 3. 0 7. 22 4. 0 8. 2	RBC: 4,530,000 WBC: 7,550 Hb. 16.8 g 1. 0 5. 0 2. 0 6. 73 3. 0 7. 27 4. 0 8. 0	RBC: 5,900,000 WBC: 10,500 Hb. 15 g 1. 1 5. 0 2. 2 6. 59 3. 0 7. 38 4. 0 8. 0	RBC: 6.040,000 WBC: 9,650 Hb. 14.9 g 1. 0 5. 0 2. 1 6. 51 3. 0 7. 46 4. 0 8. 2	1. Negative 2. Negative 3. Negative
CASE NO. 3 FROM GROUP THREE	Montevideo	0.5 gm. I.V. 9 A.M. and 0.5 gm. I.M. at 3 P.M., 9 P.M., and 3 A.M. daily for 7 days.	RBC: 5,100,000 WBC: 5,800 Hb. 13.3 g 1. 0 5. 7 2. 1 6. 46 3. 0 7. 39 4. 0 8. 7	RBC: 4,960,000 WBC: 5,600 Hb. 13.1 g 1. 0 5. 5 2. 0 6. 47 3. 0 7. 40 4. 0 8. 8	RBC: 4,670,000 WBC: 5,200 Hb. 13.7 g 1. 0 5. 2 2. 4 6. 49 3. 0 7. 41 4. 0 8. 4	RBC: 4,450,000 WBC: 7,000 Hb. 13.1 g 1. 0 5. 2 2. 0 6. 58 3. 0 7. 39 4. 0 8. 0	RBC: 4,800,000 WBC: 8,400 Hb. 13.3 g 1. 0 5. 2 2. 1 6. 63 3. 0 7. 34 4. 0 8. 1	1. Negative 2. Negative 3. Negative
CASE NO. 4 FROM GROUP FOUR	Meleagridis	100 mg/Kg/day 4 equal doses q 6 hours x 7 days.	RBC: 5,010,000 WBC: 6,800 Hb. 15 g 1. 0 5. 3 2. 1 6. 60 3. 0 7. 34 4. 0 8. 2	RBC: 5,070,000 WBC: 8,650 Hb. 15.5 1. 0 5. 4 2. 0 6. 51 3. 0 7. 42 4. 2 8. 1	RBC: 5,140,000 WBC: 8,200 Hb. 12.4 g 1. 0 5. 0 2. 0 6. 71 3. 0 7. 28 4. 0 8. 1	RBC: 4,900,000 WBC: 6,500 Hb. 14.6 g 1. 0 5. 2 2. 2 6. 60 3. 0 7. 36 4. 0 8. 0	RBC: 4,540,000 WBC: 7,600 Hb. 14.9 g	1. Negative 2. Negative 3. Negative

* SCHILLING CODE (Count 100). 1. Baso. 2. Eosins. 3. Myelos. 4. Juveniles. 5. Stabs. 6. Segs. 7. Lymphs 8. Monos.

tem. Another point of interest is the successful treatment of 2 individuals by the parenteral route, which would seem to indicate that a sufficient amount of Chloromycetin is re-excreted into the bowel following this mode of administration, so that a high enough concentration is obtained in order to effect a cure. Further studies with the parenteral route of administration, and also with Chloromycetin palmitate ester, which must be hydrolyzed in the intestine before antimicrobial activity is present are contemplated.

Summary. 1. Twenty-three of 25 chronic Salmonella carriers were successfully treated with Chloromycetin. Two cases were successfully treated using the parenteral route of administration exclusively.

2. On the basis of these studies, the optimum dose schedule for the treatment of Salmonella carriers, appears to be 100 mg./Kg./24 hrs. for 7 days.

3. No toxic reactions on any system, including the hemopoietic, were observed during, or for several months following treatment.

4. Chloromycetin appears to be a valuable adjunct in the control of chronic Salmonella carriers in institutions.

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METABOLIC EFFECTS, TOXICITY AND EXCRETION OF CALCIUM N-CYCLOHEXYLSULFAMATE (SUCARYL) IN MAN*

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The calcium and sodium salts of Sucaryl (N-cyclohexylsulfamate)** have recently been made available as non-caloric sweetening agents. There are no published studies regarding their metabolic action, toxicity or mode of excretion in man, although these problems have been thoroughly investigated in animals[5,16,22]. Accordingly, the studies to be reported were carried out in order to determine: 1. the effect of Sucaryl calcium on the metabolic balance of the healthy individual; 2. the toxic effects, if any, of a large dose given over a long period of time to healthy subjects; 3. the routes by which Sucaryl is excreted following oral ingestion and intravenous administration.

Design of the Experiments. 1) METABOLIC EFFECT: Two healthy male medical students ate and slept in an air-conditioned unit on a metabolic ward for a period of 42 days. Their daily diet consisted of twice the basal caloric requirements, 1.5 gm. of protein per kg. of body weight, 30% of total calories as fat, and 5 or 6 gm. of added NaCl. A 3-day rotation menu was provided. In the case of subject, T. P., the diet contained: protein 120 gm., fat 130 gm., carbohydrate 557 gm. and 6 gm. of added NaCl. In the case of subject, G. G., the diet contained: protein 106 gm., fat 117 gm., carbohydrate 506 gm. and 5 gm. of added NaCl. In both cases total fluid intake (food and water) was constant at 2500 cc. per day.

* Supported in part by a grant from Abbott Laboratories, North Chicago, Illinois.

** Sucaryl is the registered trademark of Abbott Laboratories.

Physical activity was commensurate with normal daily routine. No excessive exercise was indulged in.

Metabolic balances for nitrogen, sodium, potassium, calcium, phosphorus, and Sucaryl were done. Complete diets were collected for analysis on 2 occasions. Each day of the 3-day rotation diet was analyzed separately. Urine specimens were pooled for 3-day periods for analysis. Stool collections were pooled for 6 days for analysis.

Following a 12-day control period, each subject ingested 5.0 gm. of Sucaryl calcium per day for a period of 18 days. This was given in powdered form mixed with food according to the following distribution: breakfast, 1.5 gm.; dinner, 1.5 gm.; 2 P. M., 0.5 gm.; supper, 1.5 gm. Following the period of Sucaryl ingestion, observations were continued for an additional 12 days.

On admission to the hospital each subject received a complete physical examination, urinalysis, complete blood count and chest roentgenogram. Blood sodium, potassium, calcium, phosphorus, chlorides, CO_2 combining power and non-protein nitrogen (NPN) were determined on admission and at weekly intervals throughout the experiment. Liver function tests, including bilirubin, cholinesterase, gamma globulin turbidity, thymol turbidity, zinc sulfate turbidity and cephalin flocculation, were done at weekly intervals throughout the entire experiment. Endogenous creatinine clearances were also performed each week. Complete blood counts were repeated in the control, experiment and recovery periods.

2) TOXICITY: Six healthy male medical students consumed 5.0 gm. of Sucaryl calcium daily for a period of 7½ months. This was given in tablet form and was taken with meals as follows: breakfast, 1.0 gm., dinner, 2.0 gm. and supper, 2.0 gm. No attempt was made to control dietary intake or physical activity.

Before consuming Sucaryl the subjects were observed for a period of 2½ months. At monthly intervals the following observations were made: complete physical examination; urinalysis; complete blood count; electrocardiogram; liver function tests (including the same tests outlined in experiment 1); blood sodium, potassium, and NaCl; concentration-dilution test of kidney function, endogenous creatine clearance; and specific gravity of whole blood and plasma. These same studies were continued at monthly intervals throughout the 7½ months of Sucaryl ingestion. Subjects were questioned closely at the time of each examination in regard to the development of any unusual symptoms or changes in body function. In addition 24-hour urine collections were analyzed for Sucaryl at the time of each monthly examination.

3) EXCRETION: In one group of 6 healthy male medical students, 1.0 gm. of Sucaryl sodium dissolved in 10.0 cc. of normal saline was given by rapid intravenous injection. Complete collections of urine following injection were carried out for a period of 3 days. Collection periods were as follows: 0-3, 3-6, 6-12, 12-24, 24-48, and 48-72 hours. Each urine sample was analyzed for Sucaryl. Urine blanks were determined by analyzing 24-hour collections of urine obtained before injection.

The manner in which Sucaryl was excreted by the kidneys was investigated in three hospital patients. Since there is no available method for analysis of Sucaryl in blood, it was necessary to employ Sucaryl tagged with radioactive $Sulfur_{35}$. In compliance with Atomic Energy Commission requirements the patients were all ill with incurable carcinoma. Radioactive Sucaryl was administered intravenously in a solution of 5% glucose by constant infusion pump. Simultaneous endogenous creatine and Sucaryl clearances were carried out for 3 consecutive periods in each patient. Excretion of Sucaryl following oral ingestion was investigated as a part of the metabolic and toxicity studies and a fourth hospital patient was given a single oral dose of 2 gm. of Sucaryl containing 100 mg. of radioactive Sucaryl.

Analytic Methods. Methods employed for the various analysis were as follows: nitrogen by micro Kjeldahl analysis[8,13]; sodium, potassium and calcium by means of flame spectrophotometry[7,19]; phosphorus[12,25]; Sucaryl in urine and stool by a modification of the method of Audrieth and Sveda[1]; radioactive Sucaryl by the method of Taylor *et al.*[22]; serum chlorides by the method of Schales[17,18]; CO_2 combining power by the Van Slyke method[23]; blood NPN by the Koch method[9]; liver function tests: bilirubin[14], cholinesterase[15], gamma globulin[3], thymol turbidity[4,19], zinc sulfate turbidity[11], cephalin flocculation[10]; creatinine by a modification of the method of Folin and Wu[6]; blood NaCl by the method of Whitehorn[24], and specific gravity of blood and plasma[2].

Results. 1) METABOLIC ACTION: Figures 1 and 2 summarize the balance studies on subjects T. P. and G. G., respectively. On the figures are shown

the balances for nitrogen, calcium, potassium, sodium, phosphorus and Sucaryl. In Table I are shown the cumulative balances for these substances at the end of the control, experimental and recovery periods and the average daily balance during each period.

Examination of the data in regard to Sucaryl in the case of T. P. shows that all but 1.77 gm. of the 90 gm. administered were accounted for. In subject G. G., 11.35 gm. of Sucaryl were not recovered in the dejecta. Stool specimens were analyzed for Sucaryl in a laboratory outside the hospital and on several occasions the container was broken in transit with some loss of contents. This may in part explain the failure to recover all of the administered Sucaryl in the case of subject, G. G.

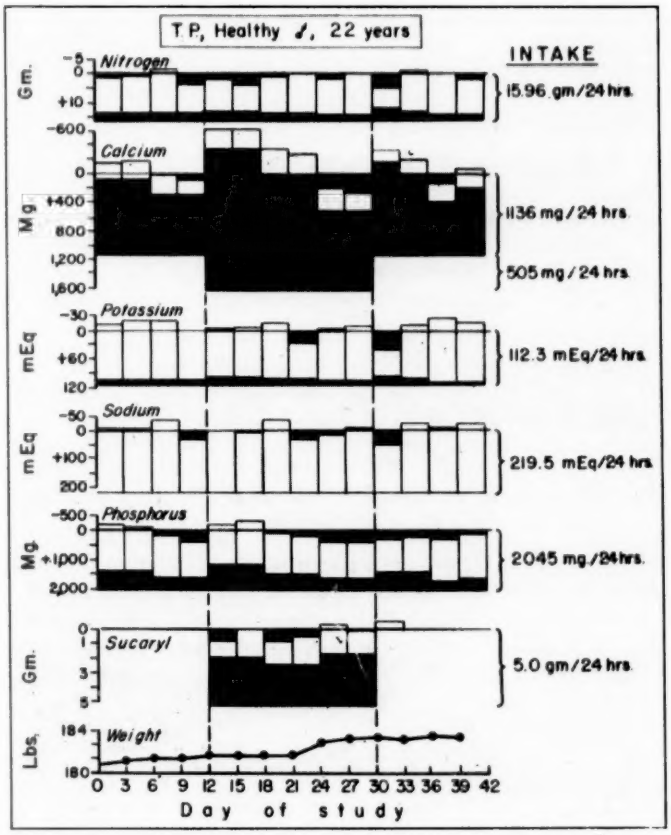

FIG. 1.—Metabolic balances in subject T.P. In this figure and in Fig. 2, intake of the metabolite is plotted by a bar graph directed downwards from the base line. Excretion in the feces is shown by a cross-hatched area, plotted up from the bottom of the intake column. Urinary excretion (blank) is added to the fecal excretion. When the sum of these two fails to reach the base line the balance is positive and the area is solid black. When the sum of fecal and urinary excretion exceeds intake the bar graph extends to the negative side of the base line. In case of either positive or negative balance, the degree can be read by the height of the solid or blank column, respectively.

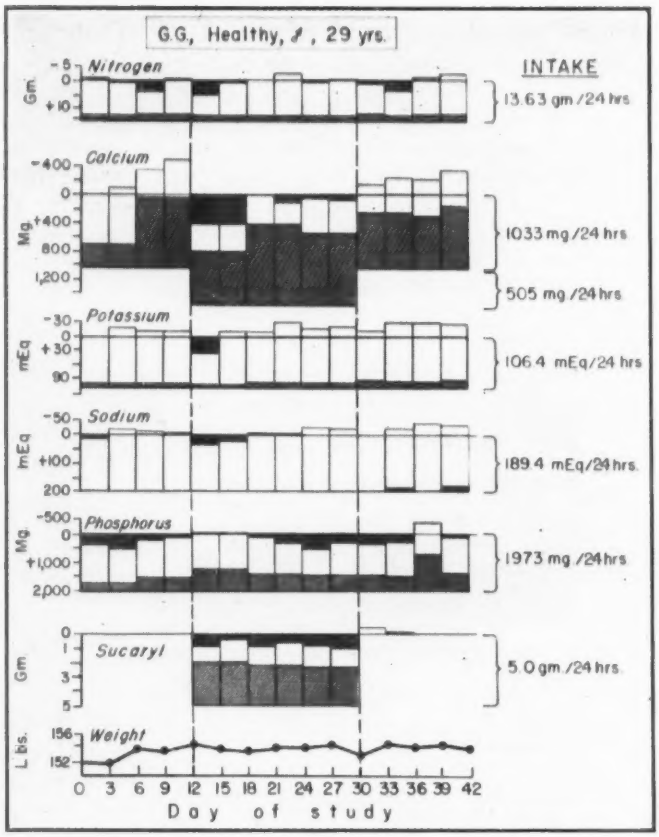

FIG. 2.—Metabolic balances in subject G.G. See subscript of Fig. 1 for interpretation of figure.

TABLE 1.—AVERAGE DAILY AND CUMULATIVE BALANCES IN CONTROL, EXPERIMENTAL AND RECOVERY PERIODS IN SUBJECTS, T.P. AND G.G.

		Subject T.P.		*Subject G.G.*	
Metabolite	*Period*	*Av. Daily*	*Total*	*Av. Daily*	*Total*
Nitrogen	Control	1.08	13.0	0.92	11.04
gm./day	Experimental	1.21	21.69	0.68	12.21
	Recovery	1.63	19.59	0.76	9.09
Calcium	Control	−60.0	−720.0	−248.0	−2958.0
mg./day	Experimental	−21.8	−392.0	171.0	3075.0
	Recovery	−92.0	−1103.0	−236.0	−2838.0
Potassium	Control	−9.20	−110.4	−15.0	−179.5
mEq./day	Experimental	−3.05	−54.9	−8.3	−150.0
	Recovery	−4.68	−56.2	−24.6	−294.4
Sodium	Control	−2.38	−28.6	−15.2	−182.4
mEq./day	Experimental	3.70	66.6	−2.65	−47.7
	Recovery	−4.10	−49.2	−12.26	−147.2
Phosphorus	Control	83.0	995.0	213.0	2554.0
mg./day	Experimental	74.3	1338.0	163.0	2931.0
	Recovery	232.0	2786.0	48.0	576.0
Sucaryl	Control	0	0	0	0
gm./day	Experimental	0.23	4.20	0.78	14.07
	Recovery	−0.20	−2.43	−0.11	−1.32

The administration of Sucaryl in the amount of 5 gm. a day had no significant effect on nitrogen balance in either subject. The diet was deliberately designed to establish positive nitrogen balance and both subjects maintained a positive balance throughout the study. Subject T. P. gained 4 pounds in body weight during the 42-day study while the weight of G. G. remained essentially unchanged.

The effect of Sucaryl on calcium and phosphorus balance was evident because the substance was administered as the calcium salt and supplied an additional 505 mg. of calcium a day during the experimental period. Both subjects were in negative calcium balance during the control period. In the case of T. P. the calcium balance became less negative in the first 12 days of the experimental period and definitely positive in the last 6 days. When Sucaryl was stopped a negative balance for calcium returned promptly. On the other hand, the phosphorus balance was positive in this subject throughout the study, but the average daily balance became significantly more positive in the recovery period.

In contrast, in subject G. G. calcium balance, negative in the control period, became positive immediately after administration of Sucaryl was begun, but promptly reverted to negative on cessation as in subject T. P. Changes in phosphorus balance were less noteworthy in subject G. G. and probably of no significance.

Both subjects were in negative potassium balance throughout the study and the administration of Sucaryl did not affect this to any great extent. Subject T. P. was in negative sodium balance in the control and recovery periods and in positive balance while Sucaryl was given. In contrast the positive balance for sodium decreased in subject G. G. during the experimental period. The changes noted in both subjects, however, were very small. Furthermore, the studies were carried out during the summer months and no measurements of electrolytes lost in the sweat were attempted.

2) TOXICITY: The effects of long-term injection of Sucaryl were investigated by repeated studies of the following organ systems: hematopoietic, cardiovascular, renal, hepatic and of the plasma. Ingestion of Sucaryl was started on March 3, 1951 and stopped on October 27, 1951. The results of all studies were within the accepted limits of normal in all individuals both in the control and experimental periods.

At monthly intervals each subject received a physical examination with particular emphasis placed on the skin and mucous membranes, ocular fundi, lymph glands, abdomen and genitalia. With the exception of one subject who developed an infection of a pilonidal sinus, no significant abnormalities were noted. All subjects maintained their usual state of good health and had no unusual symptoms except for a change in the stools. Without exception the stools increased in bulk and became mushy as long as Sucaryl was ingested. No increase in the number of bowel movements was noted. When Sucaryl ingestion was stopped, the stools promptly returned to the size and consistency typical of the control period.

3) EXCRETION: Excretion of Sucaryl from the body was studied in subjects following oral ingestion and intravenous injection.

In those subjects consuming 5.0 gm. of calcium Sucaryl daily as part of the toxicity study, analysis of 24-hour urine samples were made at monthly intervals. The results are shown in Table 2. The overall average for the 41 determinations was 1.84 gm. per 24 hours, or 37% of the daily intake of 5.0 gm. These figures are in substantial agreement with those observed in the 2 sub-

jects on the metabolic study. The data on the patient ingesting a single oral dose of 2 gm. of Sucaryl containing 100 mg. of radioactive Sucaryl are shown in Table 5.

The excretion of intravenously injected Sucaryl sodium is shown in Table 3. A dose of 1.0 gm. dissolved in 10.0 cc. of saline was injected as rapidly as possible in the anticipation that Sucaryl might prove useful as a substance for the measurement of circulation time. Only one of the 6 subjects noted a sweet taste in the mouth but the sensation was gradual in onset without a sharp end point. The data clearance was used as a convenient approximation of glomerular filtration rate. In all 3 patients, the clearance of Sucaryl exceeded the simultaneous clearance of creatine indicating that Sucaryl was eliminated both by glomerular filtration and tubular secretion. Assuming that the Sucaryl circulating in the plasma was in a completely filterable state, not bound to protein, the rate of tubular secretion was determined by standard formulae. This rate increased with increasing concentrations of plasma Sucaryl but a maximum rate was not determined in these experiments.

TABLE 2.—URINARY EXCRETION OF SUCARYL PER 24 HOURS IN SUBJECTS RECEIVING 5.0 GM. ORALLY PER DAY

Subject	*1*	*2*	*3*	*4*	*5*	*6*
Individual	1.68	3.15	1.41	2.67	2.49	1.25
Analyses	1.63	2.46	0.94	1.80	2.66	1.63
Grams per	1.99	2.43	1.13	2.69	2.83	2.34
24 hours	1.67	1.36	0.51	1.44	1.42	1.74
	1.70	1.87	0.92	1.74	1.21	1.75
	2.08	2.60	1.54	1.68	—	1.25
	1.22	2.89	2.39	—	—	1.01
	—	1.34	2.12	—	—	—
Average	1.71	2.26	1.37	2.00	2.12	1.57
Per cent of Daily Intake	34%	45%	27%	40%	42%	31%

on excretion show that 70 to 90% of the injected Sucaryl was excreted within 3 hours by 5 subjects. Within 24 hours after injection 84 to 99% of the dose was eliminated but only 36% was excreted by subject number 3. The reasons for the impaired excretion by this man were not investigated. In subject number 1, the urinary blank was not determined and the recovery could not be determined, but his pattern of excretion approximated that of subjects 2, 4, 5 and 6.

The precise mode of renal excretion of intravenously administered Sucaryl tagged with radioactive S_{35} (approximately 130 μc.) was studied in 3 patients. The results are summarized in Table 4. Endogenous creatinine

Discussion. The toxicity, physiological effects and excretion of Sucaryl have been extensively studied in laboratory animals[5,16,22]. Richards and his associates[16] have found the acute toxicity to be low. The LD_{50} for mice and rats was 10 to 12 gm./kg. when Sucaryl was given orally, 3.5 to 4 gm./kg. when given intravenously. These same observers found Sucaryl to be devoid of specific pharmacodynamic effects in a variety of experiments. No toxic effects were demonstrated when rats were given as much as 1 gm./kg. or dogs were given 2 to 4 gm./kg. for periods up to one month. However, both Richards and coworkers and Fitzhugh and Nelson[5] have noted watery diarrhea from rela-

TABLE 3.—CUMULATIVE EXCRETION OF SUCARYL IN THE URINE FOLLOWING A SINGLE INTRAVENOUS DOSE OF 1.0 GM.

	Grams Excreted by Each Subject					
Elapsed Time	*1*	*2*	*3*	*4*	*5*	*6*
30 min.	0.24	0.342	—	—	—	—
1 hour	0.45	0.569	—	—	—	—
90 min.	0.57	0.668	—	—	—	—
2 hours	0.63	0.734	—	—	—	—
150 min.	0.674	0.779	—	—	—	—
3 hours	0.703	0.807	0.32	0.89	0.866	0.925
4 hours	0.736	0.839	—	—	—	—
6 hours	0.769	0.870	0.379	0.949	0.938	0.992
9 hours	0.786	0.888	—	—	—	—
12 hours	0.806	0.900	0.405	0.981	0.987	1.089
24 hours	0.856	0.933	0.442	1.058	1.084	1.121
48 hours	0.936	1.054	0.512	1.160	1.219	1.327
72 hours	0.976	1.145	0.613	1.261	1.386	1.525
72 hour Urine Blank	—	0.234	0.258	0.294	0.402	0.681
Recovery in%	—	0.911	0.355	0.967	0.984	0.844

TABLE 4.—SIMULTANEOUS EXCRETION OF ENDOGENOUS CREATININE AND SUCARYL—S_{35} BY THE KIDNEY

	Patient		
	1	*2*	*3*
Creatinine Clearance* cc./min.	59	129	70
Sucaryl Clearance* cc./min.	181	244	151
Blood Level* of Sucaryl-S_{35} mg./100 cc.	8.8	4.06	2.45
Tubular Secretion of Sucaryl mg./min.	11.6	4.75	2.1

* Average for 3 consecutive 15 to 20 minute urine collection periods

TABLE 5.—EXCRETION FOLLOWING A SINGLE ORAL DOSE OF 2 GM. SUCARYL CONTAINING 100 MG. OF RADIOACTIVE SUCARYL

	Urine		*Feces*		*Total*	
Time Period in days	*mg.*	*%*	*mg.*	*%*	*mg.*	*%*
0–1	314.0	15.7	362.8	18.1	676.8	33.8
1–2	218.2	10.9	564.0	28.2	782.2	39.1
2–3	76.0	3.8	374.0	18.7	450.0	22.5
3–4	16.9	0.8	9.1	0.45	26.0	1.3
	625.1	31.2	1309.9	65.45	1935.0	96.7

The sputum of this patient showed no radioactive Sucaryl.

tively large doses of Sucaryl. Studies in humans[16] after a single oral dose disclosed 79.5% recovery in the urine within 7 days after a 300 mg. dose and 77% recovery in 3 days after a 200 mg. dose in one subject. Two subjects receiving 2.0 gm. excreted 35 and 47% of the dose respectively in the urine within 4 days and 2 subjects receiving 300 mg. excreted 57 and 68% respectively in 6 days[21].

The use of S_{35} labeled Sucaryl in the rat has been described by Taylor and co-workers[22]. In studies of excretion, 72% of a single intraperitoneal dose in the rat was recovered in the urine in 5 hours. Following oral administration, 40% was recovered in the feces in 4 days. Studies with repetitive doses did not disclose any evidence for retention. Catheterization of the biliary duct of dogs revealed that excretion by this route was negligible. Following intravenous injection in the rat, the distribution of Sucaryl throughout the body was not uniform until 24 hours had elapsed. The kidney showed the greatest concentration, 4 hours after injection, and Sucaryl entered the brain with difficulty.

The results of the present study are in good agreement with those reported above. No acute toxicity studies were done and the dose used in the chronic toxicity experiments was comparatively lower than those used in animals. However, a dose of 5 gm./day is in excess of the anticipated daily intake of this substance as a sweetening agent and no evidence of toxicity was discovered when it was consumed for as long as 7½ months.

Sucaryl appeared to have no apparent effect on the metabolic balances of several substances aside from those which could be attributed to the cation of the Sucaryl salt.

The results of the excretion studies confirm the findings in animals. Although the data are few, Sucaryl appeared to be excreted both by means of glomerular filtration and tubular secretion. A maximum rate for tubular secretion was suggested by the data, but the difficulty in obtaining suitable patients for study precluded further investigation of this.

Conclusions. 1. The metabolic activity of Sucaryl calcium was investigated in 2 healthy subjects who consumed 5.0 gm. per day for 18 days. Balances for nitrogen, sodium and potassium were unaffected. Balances for calcium and phosphorus were altered as a result of the calcium content of the Sucaryl. Approximately 98% (in one subject) and 87% (in the second) of the ingested Sucaryl was recovered in the dejecta. 2. The chronic toxicity of Sucaryl calcium was studied in 6 healthy subjects who consumed 5.0 gm. per day for approximately 7½ months. No toxic effects were detected by studies of the hematopoietic, cardiovascular, hepatic or renal systems. All subjects noted a tendency of the stools to become mushy but none developed diarrhea or any subjective complaint. 3. The excretion of Sucaryl was studied following oral and intravenous administration. After intravenous administration, 70 to 90% of the dose was excreted in the urine within 3 hours. Following repetitive oral administration, 37% of the dose was excreted in the feces. Renal excretion appeared to involve tubular secretion in addition to glomerular filtration.

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THE INTRAVENOUS USE OF A COMBINATION OF SODIUM PARA-AMINOSALICYLATE AND POLYVINYL PYRROLIDONE IN THE CHEMOTHERAPY OF TUBERCULOSIS

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Para-aminosalicylic acid (PAS) is a drug which has attained wide usage in the treatment of tuberculosis because, although its potency as an antituberculosis agent is relatively low, it is effective in delaying the emergence of organisms resistant to streptomycin when both drugs are used at the same time. Since the usual dosage is large (12 or more grams daily) it is given by mouth ordinarily. Gastrointestinal irritation occurs rather frequently and, therefore, medication by mouth has a definite dosage limit which varies from patient to patient. Oral PAS results in relatively low blood and cerebrospinal fluid levels which persist for only a few hours[5]. Consequently, there are times when parenteral administration is indicated: (1) when high blood concentrations are desired as in critical forms of tuberculosis; (2) when high cerebrospinal fluid levels are desired as in tuberculous meningitis; and (3) when the patient is unable to take the desired amount of drug by mouth, as in the immediate postoperative period and in the case of undue gastrointestinal intolerance.

Parenteral PAS has been used by intravenous and subcutaneous drip and large daily doses, up to 30 gm. or more, have been administered to humans without serious toxicity[1,2,5,9,13,14]. The large doses involved have made it inconvenient to give the drug by syringe injection. However, French investigators[4,6,12] have discovered that the intravenous dose could be made smaller when PAS was combined with polyvinyl pyrrolidone (PVP) without sacrificing high blood levels of PAS. PVP acts to maintain higher blood levels for a more prolonged period of time than is possible with an equivalent amount of PAS alone.

The purpose of this study is to confirm the reports of the French workers. In addition, it can be shown that PVP does not interfere with the bacteriostatic effect of PAS and that PAS, when administered intravenously as PAS-PVP, passes through the hematoencephalic barrier into the cerebrospinal fluid in adequate amounts.

Method. PAS-PVP is provided as a sterile light amber aqueous solution in 10 cc. ampules containing sodium PAS and PVP in concentrations of 25% and 3.5% respectively. For control studies a sterile 25% aqueous solution of sodium PAS and a sterile 3.5% aqueous solution of PVP were used.

Each of the test materials was evaluated for tuberculostatic effect in 5 concentrations against 10 separate strains of human tubercle bacilli isolated from patients in the Department of Chronic Diseases of the Chest at this Hospital. The evaluation and preparation of inocula was made with Dubos' liquid medium containing tween 80 and bovine albumin. The sodium PAS solution was so diluted that when 0.5 cc. volume of the diluted solution was added to 4.5 cc. of medium, concentrations of PAS ranging from 0.1 to 1000 mcg./cc. in decimal increase were obtained. The PVP-PAS was diluted to give the same concentrations as used with PAS alone. The PVP solution was diluted to give the same concentrations as used with PVP-PAS.

TABLE 1.—THE TUBERCULOSTATIC EFFECT OF PAS AND PAS-PVP

	Minimum Inhibiting Concentration of PAS in Mcg./cc.			
	At 2 Weeks Incubation		*At 4 Weeks Incubation*	
Culture No.	*PAS*	*PAS-PVP*	*PAS*	*PAS-PVP*
6–16	>1000	>1000	>1000	>1000
6–186	>1000	>1000	>1000	>1000
6–130	10	10	>1000	>1000
7–74	10	10	100	100
7–71	1	1	1	1
6–29	1	1	1	1
6–147	1	1	10	10
6–15	<0.1	<0.1	<0.1	<0.1
6–18	<0.1	<0.1	<0.1	<0.1
6–91	<0.1	<0.1	<0.1	<0.1

Note: All tubes containing PVP alone showed growth in 7 days equal to the control.

Inoculum consisted of 0.1 cc. of 7-day-old culture of tubercle bacilli adjusted to turbidity equivalent to that seen in a barium sulfate nephelometer composed of 0.5 cc. of 1% barium chloride plus 100 cc. of 1% sulfuric acid. The cultures were incubated for 4 weeks at 37° C. and readings were made at 2 and 4 weeks. Evidence of growth was the observation of turbidity equal to that seen in the drug-free control tube. The minimum inhibiting concentration was taken as the lowest concentration of drug in which no growth was seen macroscopically.

To determine the blood level curves following the intravenous injection of PAS-PVP, 6 tuberculous patients not receiving antibiotics or chemotherapy were chosen. Ten cubic centimeters of the preparation were given by syringe injection to each patient over a period of 5 minutes at approximately 8 A.M. Specimens of blood were obtained at 1, 3, 6, 9, and 12 hours after the injection. These were collected aseptically in sterile oxalated bottles and stored overnight in a refrigerator. The PAS determinations were made the following day by the spectrophotometric method of Klyne and Newhouse[8]. This procedure was repeated in the same 6 patients 2 weeks later using PAS solution. The blood level curves were compared with those obtained previously.

In order to determine whether PAS when combined with PVP passes into the cerebrospinal fluid in therapeutic concentrations, 4 patients with tuberculous meningitis were chosen. These patients were given varying amounts of PAS-PVP solution intravenously by syringe and specimens of blood and spinal fluid were obtained at 1.5 and 6 hours after the injection. Three patients were adults and 2 of these were given a single injection of 10 cc. The third adult received 2 injections of 10 cc. each one hour apart and the specimens were obtained 1.5 and 6 hours after the second injection. The fourth patient was a child weighing 17 pounds and was given only 2 cc. of the preparation.

The PAS-PVP solution has been given therapeutically to 13 patients with critical forms of tuberculosis. The dosage has been 10 cc. for adults by syringe twice a day for periods as long as a week. Seven of these patients had tuberculous meningitis of whom 6 were either stuporous or comatose. The remainder (6) were patients with pulmonary tuberculosis who could not tolerate oral PAS in adequate amounts, including one child of 20 pounds whose intravenous dosage was 5 cc. twice a day and another child of 17 pounds who received 2 cc. twice a day.

Results. The minimum inhibiting concentration of PAS in mcg. per cc.

of culture medium for 10 different strains of tubercle bacilli following 2 and 4 weeks' incubation is shown in Table 1. PAS is compared with PAS-PVP. There is no difference in the tuberculostatic concentration of PAS when it is present in the medium alone or when it is combined with PVP. PVP alone has no tuberculostatic effect.

dosage alone. With both preparations the peak is reached at 1 hour with average levels of about 23 mg. per 100 cc. with PAS-PVP compared to average levels of about 10 mg. per 100 cc. with PAS alone. Therapeutic levels (above 1 mg. per 100 cc.) persisted beyond 9 hours with PAS-PVP but persisted only a little beyond 3 hours with PAS alone.

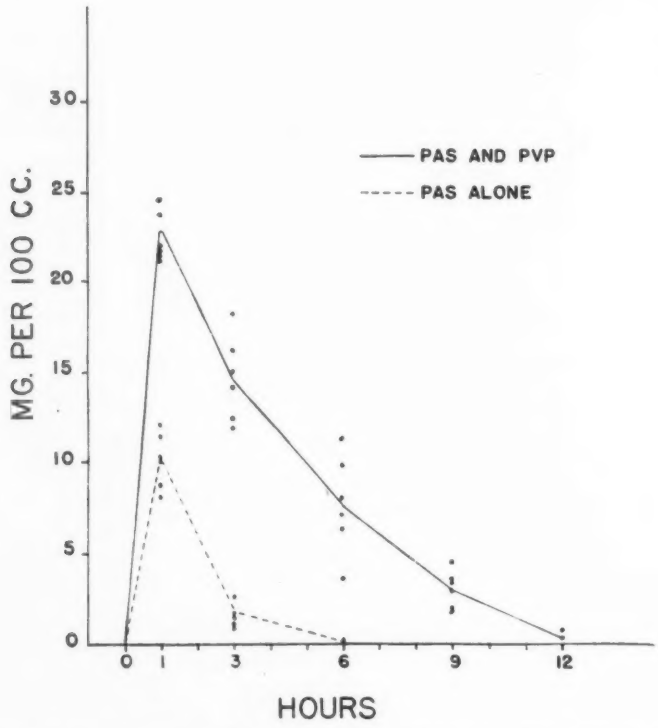

FIG. 1.—Blood PAS level curves for 6 patients given intravenous injections of 10 cc. of 25% sodium PAS in 3.5% PVP and injections of 10 cc. of 25% sodium PAS without PVP.

The PAS blood concentrations obtained with the 2 different preparations in the 6 patients used as their own controls are shown in Fig. 1. PAS levels were twice as high and lasted more than twice as long in therapeutic concentrations when the drug was administered in combination with PVP than when PAS was given in the same

The results of blood and cerebrospinal fluid PAS determinations for 4 patients with tuberculous meningitis are shown in Table 2. It is apparent that PAS passes from the blood into the spinal fluid and may be present in the latter in high concentrations. In 2 patients (A. T. and J. P.) the levels of PAS were at least as high in the cere-

brospinal fluid as in the blood at the same time. PAS blood levels were relatively low in 2 of these cases (W. T. and J. P.) at 1.5 hours after the injection and were nil at 6 hours. The explanation is not apparent to us. L. J. was given 2 doses one hour apart by error and both the blood and cerebrospinal fluid levels were high, even at 6 hours after the second dose.

The 13 patients who have thus far received therapeutic PAS-PVP showed no serious reactions. Only 4 patients received a full week of therapy as planned. Treatment was stopped prematurely in the remainder for various reasons as follows: because of discharge to sanatorium in 1 patient after 2 days of treatment, because of transitory pain in the arm in one patient during the first injection, because of difficulty in finding suitable veins in one patient (a child) after 4 injections, because of pre-existent senile psychosis in one patient after 1 injection, and because of death due to their disease in 5 patients after 1 to 5 days of therapy. In a total of over 100 injections there has been complaint of pain once, mild dizziness twice, and venous thrombosis once.

TABLE 2.—BLOOD AND SPINAL FLUID CONCENTRATIONS OF PAS FOLLOWING INTRAVENOUS PAS-PVP

Patient	*Dose of PAS-PVP in cc.*	*Time Specimen Obtained After Last Injection in hours*	*Blood Conc. mg./100 cc.*	*CSF. Conc. mg./100 cc.*
W. T.	10	1.5	5.7	1.7
		6.0	0	0
L. J.	10 cc. followed by 10 cc. 1 hr. later	1.5	22.0	17.6
		6.0	11.5	10.3
A. T.	10	1.5	16.2	16.5
		6.0	3.4	5.1
J. P. (child)	2	1.5	11.1	13.4
		6.0	0	—

Discussion. PAS has been used intravenously in large daily doses by various investigators without significant toxicity [1,2,5,9,13,14]. PVP has likewise been used intravenously in large amounts as a plasma expander without significant toxicity[3] although some of this colloid is stored in the fixed phagocytes of the body[7,15] and, therefore, its prolonged administration may be contraindicated. There is no reason to suppose that the short term use of the relatively small amounts of PAS and PVP employed in this investigation would result in untoward reactions. However, one must be aware of the possible development of alkalosis and hypopotassemia when one uses parenteral PAS therapy[10].

In France, Durel[4] and Pellerat *et al.*[12] have been investigating the use of PVP to prolong the action of various drugs such as insulin, PSP, penicillin, local anesthetics, and salicylates. The use of PVP with salicylates led to its use with PAS and, in 1950, a short note on the work of Brun, Pellerat, and Kalb appeared in the section on foreign letters of the Journal of the American Medical Association[6]. It was reported that PAS-PVP was given intravenously to 20 patients once or twice a day in doses of 10 to 20 cc. for as long as 3 months without untoward results. This has been confirmed by the present investigation for short periods of treatment.

Pellerat *et al.*[12] suggest that PVP forms a molecular complex with various drugs and, since PVP is a colloid, it retards both absorption and excre-

tion of the bound drug upon injection into the tissues. When salicylates are given by mouth prolongation of salicylate blood levels occurs even when PVP is given separately intravenously at the same time[4] so that the formation of a molecular complex apparently takes place within the body as well as *in vitro*.

In the United States, Moss *et al.*[11] have reported recently that PVP prolongs the action of some barbiturates but not all. The use of PVP for the purpose of prolonging the action of drugs has received only scant attention in this country. A multitude of uses can be envisaged for combinations of PVP with various drugs and the entire matter deserves thorough evaluation when one considers that insulin-PVP has an action as prolonged as that of protamine zinc insulin[4].

The use of PAS combined with PVP for parenteral therapy has some merit in that high blood and cerebrospinal fluid levels of PAS may be maintained with small amounts of drug. There is a definite advantage to the patient and to the nurse since the drug may be administered by syringe injection rather than by drip. Further study is required to determine whether larger doses may be given intravenously with safety, to rule out a cumulative effect and toxicity with more prolonged administration, and to evaluate the use of this combination in dilute form for subcutaneous drip.

Summary and Conclusions. The intravenous use of a preparation of 25% sodium PAS in 3.5% PVP has been compared with the intravenous use of 25% sodium PAS alone. It has been shown that PVP does not interfere with the tuberculostatic efficacy of PAS *in vitro*. PVP acts to maintain higher and more prolonged blood concentrations of PAS and it does not prevent PAS from passing into the cerebrospinal fluid in adequate amounts. PAS-PVP has been used therapeutically for periods up to 1 week without significant toxicity. This preparation has the advantage that it may be given by syringe injection and smaller amounts of PAS are needed to establish high concentrations of the drug in the blood and cerebrospinal fluid.

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PROGRESS
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THERAPEUTICS

UNDER THE CHARGE OF
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THE SURGERY OF ACQUIRED VALVULAR HEART DISEASE

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SURGERY of the valves of the heart has established itself in the past 5 years as an integral part of surgical practice. The road has been long since 1883, when Billroth stated "Let no man who hopes to retain the respect of his medical brethren dare to operate on the human heart"[14]. This dictum did not stifle all investigation for, in 1882, Bloch[17] had demonstrated successfully the suture of wounds of the heart in animals and proposed the procedure in man. Samways[74], in 1898, anticipated "that with the progress of cardiac surgery some of the severest cases of mitral stenosis will be relieved by slightly notching the mitral orifice and trusting to the auricle to continue the defense, (namely, the prevention of regurgitation). In 1902, Brunton[19], impressed with the hopelessness of medical attacks on the problem of severe mitral stenosis, suggested study of a surgical approach. Lane wrote[59] that, about 1890, he had gone into the matter fully and concluded that operation was feasible. He mentioned it to his colleague L. E. Shaw, but there the matter ended. The explanation probably lies in Shaw's comment[76] "It is possible to do many things that are useless, and some things that are harmful". General criticism of Brunton's suggestion was based on doubt of its efficacy and also on technical difficulties.

Investigators began to study the experimental production of valvular lesions: MacCallum[64], Cushing and Branch[23], Bernheim[9], Schepelmann[75], Haecker[46], Tollemer[82], Carrel and Tuffier[21]. Bernheim's studies[9], in 1909, were the first undertaken with the primary purpose to experiment with an operative procedure in animals that might be applied later to man. In 1912, Tuffier[83] operated on a young man with aortic stenosis, dilating the orifice by insertion of his finger, invaginating the

wall of the aorta. The patient survived. Doyen[31], in 1913, attempted to operate on a patient considered to have mitral stenosis but operation disclosed an interventricular communication. In 1923, Cutler[25], who previously had been working with animals, successfully completed the first surgical attack on a case of mitral stenosis. He used a valvulotome and approached the valve through the left ventricle. The patient was improved and lived for four and one half years. To 1928, nine more cases were operated upon, all for correction of mitral stenosis: 6 by Cutler and his associates[24,26], using a tenotome or valvulotome, and all succumbing from hours to 6 days postoperatively; Allen[1] using a cardioscope in the left auricle, with an operative death; Souttar[78] with finger fracture via the left auricle with success; Pribram[73] using a valvulotome, the patient dying. The work of Powers[72] indicated that the poor results that followed section of the mitral valve were due to the effects of the acute mitral regurgitation produced.

Until 1945, no further valvular surgery was performed. In 1948, the Bland-Sweet[16] procedure was proposed: an anastomosis between a branch of the right inferior pulmonary vein and the azygos vein. The purpose was to divert blood from the pulmonary circuit into a systemic vein, thus causing some blood to by-pass the stenotic mitral valve. In France, d'Allaines and his associates[27] independently performed a similar procedure. It was recognized by both groups that this procedure was at best a compromise and not a cure, and the direct approach to the valve was preferred on its development. Bailey[4], Harken[49], and Smithy[77] were in the forefront of this evolution. The most favored approach is now the left auricular appendage, since it leads directly into the wide opening of the mitral funnel and its stenotic orifice. Further, the chordae tendinae do not interfere, and there is rarely any serious disturbance of rhythm or function produced. Finger-fracture valvuloplasty[48,49] (Harken) entailing blunt dissection of fusion bridges with the finger is the procedure of choice. Bailey and his group[4,5,6] prefer commissurotomy, guided incisions in the region of the obliterated valve commissures. All procedures are directed at reducing the stenotic block with greatest possible restoration of valve function, and avoidance of induced regurgitation to a minimum. Progress was made possible by general advances in surgery during World War II, improvements in anesthesia, and development of chemotherapy and the antibiotics[3]. Furthermore, the development and application of physiological techniques, by cardiac catheterization led to studies of the abnormal circulatory patterns resulting from valvular dysfunction and their change after surgery.

The degree of narrowing of the mitral valve varies greatly, from a slight obstruction to blood flow into the left ventricle, to the extreme of a slit-like opening compared to a fish-mouth or button-hole. The circulation must compensate by the adjustment of pressure and flow across the mitral valve and the development of increased resistance in the lungs. The studies of Lewis and associates[61] led to the following analysis of the disturbed physiology in mitral stenosis. The pressure in the left auricle and pulmonary capillaries must rise if blood flow is to remain the same[29,40,51]. The pulmonary arterial pressure rises also to preserve the gradient needed for flow[29,32]. At a normal mitral valve area of 4 sq. cm., normal flow can be accomplished at a low head of pressure, and marked increase in flow is possible with small increments in left atrial pressure[39,40]. In mild stenosis with a valve area of 2.5 sq. cm., normal resting flow can be maintained at a relatively

low pulmonary "capillary" pressure, but any increase in flow, as with exercise results in marked increase in such pressure, that may equal the osmotic pressure of the plasma[42]. Progressive increase in pressure becomes necessary to secure a given flow as the valve narrows. As the stenosis increases toward a valve of 1.0 sq. cm. or smaller, a critical point is reached, for a left auricular pressure approaching plasma osmotic pressure (25 mm.Hg) becomes necessary to maintain a barely normal resting flow. The maintenance of pressure appreciably above this level for any length of time will be followed by pulmonary edema[42]. To avoid this, a fall in blood flow occurs as a second compensation. There occurs a linear decrease of cardiac index (cardiac output/sq.m. body surface) as the valve narrows to an area of about 1.0 sq. cm., the point where subnormal levels are reached.[61]. A resting state requiring such high capillary pressures is apparently the stimulus for the development of increase in pulmonary arteriolar resistance[29]. This tends to decrease the output of the right ventricle and to some degree protects the pulmonary capillaries from surges of pressure[29]. But while protecting the capillaries, it further decreases cardiac output and increases the work load of the right ventricle, leading to its enlargement and eventually its failure. In some instances, this resistance may become so great that it requires more work to maintain flow through the lung vessels than through the stenotic valve[63]. Under these circumstances, pulmonary arterial pressure may increase out of proportion to pressure in the pulmonary vein, and may approximate systemic arterial pressure[32,56,63]. The increased resistance of the lung bed is due to changes in the small vessels plus vasoconstrictor factors not well understood. The vascular changes[60,69] consist of the intimal thickening of arteriolar sclerosis, and medial changes of the arterioles that may be reversible[60]. Dilatation of capillaries and thickening of capillary basement membrane are also present. There is no close correlation between the degree of mitral stenosis and the degree of these anatomic changes, other than they are unlikely without severe stenosis. Severe stenosis, however, may exist without them. High degrees of pulmonary resistance may regress to normal over a period of 6 to 12 months after operation[30].

Studies[32,43,63] during and after exercise indicate additional difficulties in the patient with mitral stenosis. In some the cardiac output falls further[52]. Since the resting output is the maximum that can be maintained consistently by the heart, exercise causes further decrease, just as in frank myocardial failure[32,81]. Arteriovenous oxygen differences are markedly increased, out of proportion to the rise in oxygen consumption[32]. Oxygen consumption per liter of ventilation frequently falls[22,32]. The mean pulmonary arterial pressure usually rises[32,52], this in contrast to the fact that normally a rise in cardiac output to three times its resting level can be effected without change in pulmonary arterial pressure (Cournand). It should be recalled that these findings are similar to those found in patients with cardiac failure[37]. Elevation of right atrial pressure, increase in the residual volumes of blood in the right ventricle[10] and increase in right ventricular end diastolic pressure[37] are the only additional findings in right heart failure.

Attempts have been made to relate specific symptoms of mitral disease to the physiologic disturbances noted.

Exertional Dyspnea. It is felt by most reviewers[2] that this symptom arises both from pulmonary congestion and decreased cardiac output. Lewis *et al.*[61] divided patients with mitral stenosis into groups, based upon 2 factors,

mitral valve area and pulmonary arteriolar resistance. The first group encompasses those with stenosis mild enough to enable compensation by alteration in pressure and flow alone. The other groups consist of those with valve areas of 1 sq.cm. or less, where simple compensation is no longer possible, and increases in pulmonary arteriolar resistance are (1) too slight to diminish pulmonary congestion (2) just enough to avoid episodes of congestion and (3) so great that the right ventricle fails. Mild exertional dyspnea only is noted in Group 1. In Group 2, respiratory symptoms were outstanding: severe exertional dyspnea, paroxysmal nocturnal dyspnea, hemoptyses, recurrent bouts of pulmonary edema. In Group 3, the balance between cardiac output and pulmonary resistance is such that patients could work at light occupations without severe dyspnea, could be relatively free of paroxysmal respiratory symptoms, and yet have few signs of failure. The last group had severe dyspnea, grossly enlarged hearts and signs of congestive failure. The dyspnea here seems related to the reduced cardiac output or the high pulmonary artery pressure which is present, and resembles the dyspnea seen in pulmonary vascular disease. Sometimes, when the right heart fails, there is reduction of the pulmonary symptoms, and their replacement by liver enlargement and peripheral edema.

Paroxysmal Nocturnal Dyspnea and Pulmonary Edema. Altschule[2] ascribes attacks to frank or incipient edema, while others may result from changes of position in severe dyspnea or orthopnea. In a series studied by Lewis *et al.* [61], 14 of 16 patients had valve areas of 1 sq.cm. or less, emphasizing the importance of this degree of stenosis in the production of this symptom. A common denominator in many cases of mitral stenosis with episodes of pulmonary edema is the elevation of pulmonary "capillary" pressure above the plasma osmotic pressure[42]. Two factors that may contribute to this rise are increased return blood flow, demanding higher pressures in the left auricle and lung vessels, and tachycardia which demands a greater flow through the mitral valve per unit of time, and thus higher pressures too. The increased blood volumes that accompany sleep[71] may be the stimulus to acute increases in pulmonary congestion and cause paroxysmal nocturnal dyspnea. Other patients, severely orthopneic, may experience this symptom from a change in position.

The situation during exercise is ideal for the development of pulmonary edema in tight mitral stenosis, because of the marked increase in return blood flow in the presence of tachycardia. A vigorous right ventricle is capable of flooding the lungs, and increasing the intravascular pressures because of the reduced flow-off capacity of the mitral valve.

Hemoptysis. Some patients may experience recurrent episodes of expectoration of blood, often a cupful or more[84]. This may occur without preceding or associated dyspnea. It may follow an attack of cough, but more commonly, other signs of pulmonary congestion are absent at the time. Despite these clinical facts, a group studied by Lewis *et al.*[61] had severe respiratory symptoms. A strong right ventricle here, too, congests the lungs acutely, and ruptures dilated channels which serve as collaterals between the high-pressure pulmonary veins and the veins in the larger bronchi that eventually empty into the low pressure azygos system[36]. The occurrence of hemoptysis may lower pressures in the pulmonary venous system so that pulmonary edema rarely is associated.

Hemoptysis also occurs under other circumstances in mitral stenosis. Pulmonary infarction due to embolus or

local thrombosis is associated with blood spitting, but associated findings in the lung serve to distinguish it from the type of hemoptysis referred to here. Respiratory infections and the blood streaking in pulmonary edema have their distinctive features.

Despite the importance of the physiologic data cited in the previous paragraphs, it is important to note that a study of several groups of patients evaluated by physiologic techniques reveals exceptions to all the general findings described[32,61,63]. Some patients with severe changes had few clinical symptoms, others with severe disability had mild changes. There is no single factor from which to determine whether severe mitral stenosis exists or that severe organic changes of the pulmonary circulation or lungs are present[35]. There is no absolute or invariable correlation with cardiac output. A trend to increased pulmonary arterial pressure and pulmonary resistance with increased grades of stenosis is generally noted. But even here, discrepancies are found, and these associations did not coincide always with chronic dyspnea or even attacks of pulmonary edema. It appears, therefore, that objective studies may be helpful, and in obscure cases, necessary (Harken); but routine catheterization can not be considered an absolute requisite for decision regarding surgery at this time.

There is no simple way to select patients suitable for operation. It entails complete evaluation of the clinical picture, in particular the degree of chronic disability as regards dyspnea, and the tempo with which it is developing.

The diagnosis of mitral stenosis *per se* ordinarily presents little difficulty. The characteristic rumbling diastolic murmur, with its presystolic crescendo, ending in a sharp, snapping first heart sound is easy to recognize. The accentuated pulmonary second sound reflects the increase in pulmonary pressure. The increased size of the left auricle, the pulmonary artery[50], and the right ventricle are additional findings of diagnostic significance. Recent studies suggest that size of the left atrium is estimated best by left lateral teleroentgenogram with barium in the esophagus[54]. One cannot draw any fine conclusions of the degree of stenosis from the intensity of the murmurs, and in fact, in the presence of an extremely tight mitral stenosis, no murmur may be heard. Rough correlation is found between intensity and duration, and degree of stenosis. (Levine and Harvey).

There is agreement on the management of mitral stenosis where, aside from the characteristic murmur, these patients have no symptoms or other signs of their disease. Surgery is not indicated under these benign circumstances[5,8,14,28,49,67]. Actually, the stenosis is not always progressive, and some patients may attain ripe old age without difficulty. In the Bland and Jones[15] series of 1,000 children followed for 20 years after rheumatic fever, 117 acquired a pure form of mitral stenosis, but only 12 progressed to a state of severe pulmonary hypertension.

Those cases of stenosis whose course is characterized by episodes of pulmonary edema or gross hemoptyses or both are ideally suited for surgery. They have relatively normal sized hearts, whose strong right ventricle takes care of its increased burden during exercise very well, but it goes beyond the ability of the mitral valve to accept all the blood provided it. The dramatic nature of these symptoms attracts attention to these patients and their plight relatively early, so that help too can be provided early in the course of events.

The choice of other types of patients for surgery is not absolutely delineated. It suffices at the start to state that the chances of striking benefit decrease as

the duration of symptoms lengthens[3]. Obviously, little benefit can be expected when the myocardium is damaged beyond possible return to normal, and irreversible changes in the small lung vessels and the liver may remain.

A number of patients reach a level of dyspnea and fatigue on effort which is not disabling, and with or without medical measures remain at this level. These stationary cases seem best carried along on a medical regimen, but if this static disability is unacceptable to the patient, surgery may be offered[5,48].

Another group despite the best therapy slowly loses ground. The rate of deterioration varies greatly. Dyspnea, orthopnea, cough and ease of fatigability increase. There is need for more intense restriction of sodium, more frequent use of diuretics, and more frequent periods of bed rest to prevent or control failure. The progressive character of the disability provides the cue to surgical treatment here. The life expectancy of these patients is hazardous and surgery should not be withheld long after the progressive pattern becomes clear. Changes in the valve are usually complete at this time, and the progression represents gradual myocardial breakdown.

Harken[48] uses the classification of 1, benign; 2, statically handicapped; 3, progressive; 4, terminal or completely incapacitated. The O'Neill[68] grouping is essentially the same: 1, asymptomatic; 2, statically incapacitating; 3, progressively incapacitating; 4, terminally incapacitated; 5, irretrievable. It is not possible on clinical grounds to distinguish between patients for Groups 4 and 5, but Group 5 is used by Bailey and his associates for those cases which fail to improve after adequate commissurotomy. Harken and Bailey have been operating upon some of the "terminal" cases. A mortality rate of almost 35% was reported by Harken[48], and this rate might have been expected to continue high for these are dying patients. More recently, it has been reduced to 20%. By comparison, of a series of 19 patients in this group who refused surgery, 90% were dead in one year, 80% within 6 months[48]. This would indicate that some in this totally incapacitated group can be salvaged to some degree. Although improvement in this group, when it does occur, is less dramatic, no patient who survived operation was made worse[48]. These cases have progressed evidently beyond the point where a mechanical approach to their problem suffices to correct the situation. The state of the myocardium is now of even greater importance, as is that of the lung vessels and liver.

CONTRAINDICATIONS: RELATIVE AND ABSOLUTE. Two absolute contraindications to surgery are active rheumatic carditis and subacute bacterial endocarditis. In the presence of rheumatic activity, the myocardial involvement may be the important factor in the progressive pattern of disability rather than the mechanical burden of the narrowed valve. Furthermore, the effect of surgery on the active disease, as well as the effect of active disease on the valvuloplasty are not clarified.

An interesting and important sidelight is the frequency of Aschoff nodules in atrial biopsies taken at operation. Ellis[35] reported 45% in their cases, Kuschner[57] 36%, Biörck[12] 33%, Janton[56] 16%, Griffith[45] 25%, Hurwit[53] 20%. These were found despite routine clinical and laboratory studies to exclude cases with active rheumatism. In the Biörck[12] series, neither sedimentation rates nor antistreptolysin titers were helpful, but definitely elevated antistreptolysin titers seemed the most important signals. What these auricular findings mean is difficult to assess at this time. Those with positive biopsies appear to do as well as the others.

Those with small hearts and sinus rhythm gave positive findings in 90% of one series[35], yet results were excellent. There appeared to be a low incidence in those with auricular fibrillation at any age[35]. Although there is no proof that rheumatic endocarditis of this type is a menace to the operation, definite conclusions should be withheld. Unequivocal rheumatic activation had not been reported until recently. Griffith[45] mentioned 2 (of 74) cases without detail. Hurwit[53] referred to 3 exacerbations, none of which were in patients with Aschoff bodies in their atrial biopsies. These findings emphasize the known fact that subclinical rheumatic activity may persist for many years after termination of its clinical counterpart. The entire problem of rheumatic activity in the adult needs evaluation.

In the life cycle of mitral stenosis, it takes 5 to 15 years before fully developed stenosis evolves. Whether the factors involved are repeated attacks of a more or less continuous rheumatic process or merely contracture of a scarred valve, or both, is not known. Because of this time relationship, few cases present clear indications for surgery before the third decade. Since the possibility of active carditis is greatest in the younger age group, they should not be operated upon unless the indications are most urgent. The auricular biopsies show a reduction in the number of positive cases with increasing age, confirming the general impression. Few patients over 50 years need be considered for surgery. This is not invariably true, as when rheumatic fever appears late in life and symptoms develop correspondingly late. The patient's general state rather than chronological age may be determining. In general, the older the patient, the more rigid should be the criteria of selection and the fewer the variables permitted to influence decision[55].

The valve lesion *per se* ideally should be a "pure" mitral stenosis. A mitral regurgitation, if marked in degree, is a contraindication. Although present day techniques avoid the overwhelming regurgitations that followed section of the anterior leaflet, some degrees of regurgitation may result. This is increased by an enlarged left ventricle, usually present with organic mitral insufficiency and may reduce critically left ventricular output. The diagnosis of mitral regurgitation in the presence of mitral stenosis may be most difficult. Gorlin *et al.*[41] in his studies emphasized the importance of fatigue and weakness as striking symptoms in patients with mitral insufficiency of moderate degree. He related this to the extremely low, effective (aortic) cardiac output and poor tissue blood flow seen in many of these patients. Most of his patients with regurgitation had mild mitral stenosis, yet in contrast to patients with similar degrees of pure stenosis, all were incapacitated by symptoms. Fatigue was the major symptom, dyspnea was less prominent. Of course, if the left ventricle fails, one might expect dyspnea, orthopnea and cough to appear. And patients with severe stenosis and right ventricular failure do complain of fatigue on exertion, as do the patients with associated regurgitation, but severe dyspnea often overshadows all other exertional complaints.

As regards the systolic apical murmur considered indicative of mitral regurgitation, positive and negative errors are possible. Apical systolic murmurs of Grades 1 and 2 may or may not mean mitral regurgitation[41]. The greater the intensity of the murmur, the more likely does it indicate an insufficiency. High pitched musical murmurs are common in regurgitation. In general, there is rough correlation

between the grade of the murmur and the volume of regurgitated blood[41]. One should except extreme degrees of incompetence where the murmur may be very faint. Regurgitation has been found at the operating table without any murmur having been heard previously[38,41,48]. A tricuspid insufficiency may occasionally produce an apical systolic murmur and should be guarded against.

Roentgen-ray studies can be very helpful in the diagnosis of mitral regurgitation. The left auricle is likely to be larger than in pure mitral stenosis, possibly related to the high swinging pressures, but since this is only a matter of degree, it is a sign of limited value. The giant auricles occasionally seen represent almost always the combined effects of stenosis and regurgitation. Systolic pulsation of the left auricle in mitral regurgitation reflects the increase in size during ventricular systole, and can be a valuable sign. Elkin *et al.*[34] have studied this phenomenon recently. Two positions are useful for visualizing the auricular expansion, the anteroposterior and the right anterior oblique position. The right cardiac border as seen in the anteroposterior position, may present a double contour, a cranial (left auricle) and caudal (right auricle). These contours may alternate in movement, giving a seesaw motion. The upper contour expands laterally in ventricular systole as the left atrium is expanded by the regurgitation stream. In the right anterior oblique position with barium in the esophagus, a posterior pulsation by the left auricle with ventricular systole is seen, simultaneously with the inward ventricular movement in systole along the anterior border of the heart. Although expansion of the left auricle is strong evidence of mitral regurgitation, its absence does not exclude the possibility. Variables that may be important are the size of the auricle, the flexibility of its wall, the rate of diastolic filling from pulmonary veins, and the presence of mural clot[34]. Errors of interpretation may arise when the posterior aspect of the heart in the right anterior oblique position is pushed back by a large right ventricle[34]. A vigorously expansile right auricle in tricuspid insufficiency may transmit an impulse to the left auricle also[34]. Electrokymography may have value in recording auricular expansion[70], but in auricular fibrillation good tracings are rare.

In mitral regurgitation, the left ventricle enlarges in an attempt to maintain an adequate aortic output despite the regurgitant blood flow. This contrasts with the normal or small left ventricle in "pure" mitral stenosis, and recognition of this enlargement, in the absence of aortic disease or hypertension, points to the presence of mitral regurgitation. Careful fluoroscopy is important, but it is often difficult to recognize when the right ventricle is markedly enlarged. With considerable experience, a greatly enlarged right ventricle with its clock-wise rotation, and accompanying posterior rotation of the left ventricle can be detected.

Along these lines the electrocardiogram may be of value. In a patient with mitral disease, the electrocardiographic pattern of right axis deviation, right ventricular hypertrophy or right ventricular strain point to dominance of the stenotic lesion. The presence of a combined hypertrophy or strain pattern suggest both stenosis and regurgitation of significance. Deviation of the electrical axis to the left or the pattern of left ventricular hypertrophy indicates predominant regurgitation in the absence of other explanation.

Biörck[11] believes in the value of angiocardiography in all problematic cases of mitral disease to obtain an exact determination of the size of the left auricle and ventricle and the degree

of mitral regurgitation. Increasing experience may make this a valuable tool in a difficult case.

The value of pulmonary "capillary" pressure tracings in the diagnosis of mitral insufficiency is still unclear. Lagerlöf and Werkö[58] found an unusually early and high systolic pressure rise (V wave) was indicative of mitral regurgitation. Later studies[33] from the same laboratory were more skeptical. Biörck's[11] experience has been less favorable than originally expected. Gorlin[41] felt that the large V wave often indicated regurgitation, but was not a good measure of its degree. Draper[32] *et al.* stated that physiologic methods alone do not permit clear differentiation between mitral stenosis and insufficiency.

It would appear, then, that careful physical and fluoroscopic examination remain the best guides to the importance of any mitral regurgitation present in a particular case, with the electrocardiograph giving additional aid. If the stenosis is adjudged the dominant lesion, and minimal or no left ventricular enlargement evident, surgery may still be indicated. The possibility of a more equivocal surgical result is suggested however. Despite best attempts, there may still be striking discrepancy between the clinical impression and the actual regurgitant jet that the surgeon notes. The surgeon's impression too may not be wholly accurate because of low intraventricular pressure at time of operation, yielding little or no jet, and a large ostium too producing a feeble jet.

Aortic insufficiency also presents contraindication if it has caused appreciable left ventricular enlargement and wide pulse pressures. Grades 1 and 2 diastolic murmurs heard along the left border of the sternum frequently represent the Graham Steell murmur heard in pulmonary hypertension, rather than aortic insufficiency. They are ascribed usually to pulmonic insufficiency, but recent studies suggest this may not always be the interpretation[66].

Aortic stenosis causing left ventricular enlargement presents an absolute contraindication, unless corrected at the same time.

Tricuspid stenosis may make the operation more hazardous, but minor degrees of tricuspid regurgitation do not rule out the procedure. Lukas and Dotter[63] found the typical pattern (large peak-plateau pressure rise occurring after QRS) of tricuspid insufficiency in the right atrial tracings of 8 subjects, the diagnosis having been made clinically in only one patient.

Extreme enlargement of all cardiac chambers is an absolute contraindication, and in general, the larger the heart, the poorer the result. Congestive failure that cannot be influenced by bed rest and the most intensive therapy also opposes surgery[15].

A calcified mitral valve *per se* presents no contraindication[18,38] and need not necessarily mitigate against a good result. In some instances, a satisfactory reconstructive effort may not prove possible[56]. The danger of embolism from a calcific plaque is also present.

Auricular fibrillation presents a contraindication only when the ventricular rate cannot be controlled. Sixty percent of Harken's cases, and over 50% of Bailey's cases were fibrillators. The eventual result appears to be as good as in those with normal sinus rhythm. The possibility of embolization is greater and the immediate hazard of operation increased thereby. As of May 1951, Bland's collected series[14] of 352 patients revealed an incidence of 6% of emboli, some with auricular fibrillation, some with chronic failure. Changes in technique appear to have been responsible for reduction of the frequency of this event during the past 2 years. No attempt is made to shell out large cast thrombi from the

atrial appendage. Smaller thrombi are permitted to be flushed out when the appendage is opened. Of importance appears to be the practice of making pressure on the carotid vessels[44,47,48], or better yet, isolating the left common carotid artery and the innominate artery, and obliterating their flow temporarily, when the finger is in the auricle and the danger of emboli is greatest[7]. Some surgeons use heparin when extensive clot is found at operation[45,48], beginning 5 or 6 hours after operation and continuing for 3 to 5 days. Most surgeons do not use anticoagulants.

The occurrence of repeated emboli in the greater circulation in a patient with mitral stenosis may be considered an indication for mitral surgery. Since the procedure entails ligation and amputation of the auricular appendage, a favorite site of thrombus formation is eliminated. Also, enlargement of the mitral orifice reduces the factor of stasis in the auricle and reduces the tendency to recurrent thrombus formation. In 22 cases with cerebral, visceral or peripheral emboli reported by Janton[56], no recurrent embolic episodes were seen postoperatively, the longest after 3 years.

Most patients are digitalized before operation. Adequate preoperative sedation is important, opiates and barbiturates being used. Atropine or scopolamine is given before induction, to reduce secretions in the bronchial tree and to minimize vagal reflexes. General anesthesia, ether or ether and cyclopropane, is used. The induction period should be as smooth as possible, to avoid tachycardia with its possibility of producing shock by reducing cardiac output further or pulmonary edema by further increasing pulmonary vascular pressures[62]. Sinus tachycardia with ether is often controlled by small amounts of cyclopropane[62]. Lightening the plane of ether anesthesia alone may suffice. Many anesthetists use secobarbital for induction. Hypotension due to vasodilatation caused by anesthetic agents should be avoided if possible, by inducing anesthesia slowly and maintaining light planes of surgical anesthesia. It presents a serious problem in patients with fixed or falling cardiac output and should be counteracted if it develops. Blood loss should be replaced promptly. Intra-arterial blood may be of benefit in prolonged hypotension. Vasopressor drugs, such as l-norepinephrine, have value, and can be used.

Cardiac arrhythmias may present a problem during the operative period. Prophylactic use of quinidine, procaine or procaine amide is not a practice. In most cases the arrhythmias can be related to anesthetic management, except for direct manipulation of the heart. Pericardial incision, clamping of the auricle and auricular appendectomy was followed by irregularity in many patients (33% of Spiegl's series)[79]. Placing of auricular sutures caused auricular premature contractions in 80%, ventricular premature contractions in 8%. Palpation of the inner aspect of the heart caused more irritability than any other procedure except valvuloplasty itself, that of the ventricular endocardium more so than the auricular endocardium. Ventricular premature contractions or ventricular tachycardia are seen in almost every case at the time of valve fracture, but this is usually transient and does not require specific treatment. On some occasions, ventricular tachycardia may last for longer periods, when procaine amide should be used[65]. Ventricular fibrillation rarely may occur. Cardiac massage and electrical defibrillation are the treatments of choice, although Spiegl[79] reported a case that reverted to regular sinus rhythm following bathing of the epicardium with 1% procaine. Many surgeons routinely bathe

the pericardial sac with procaine, but its efficacy in the prophylaxis of arrhythmias is not proven. Reflex vagal effects upon the heart may produce bradycardias, due to sinus bradycardia or nodal rhythm. Intravenous atropine may be of benefit, but is not without danger. It appears advisable to oxygenate and hyperventilate the patient first before using atropine[62]. Prostigmine methyl sulphate, 0.25 mg. intravenously, has been claimed effective in the treatment of tachycardia[79]. Epinephrine is of value in cardiac standstill, in conjunction with massage.

In the immediate postoperative period, a number of complications may appear, related to the operative procedure[56]. A pericardial friction rub, due to a "traumatic" pericarditis is heard frequently and may last 10 days. The usual post-thoracotomy pain occurs in almost all patients, lasts 7 to 10 days and is relieved by sedatives. Another type of pain, pleuropericardial, typical of that seen in acute pericarditis develops in about 30% of cases, most often during the second week postoperatively. It may occur or recur at any time in the ensuing 6 months. The usual location is substernal, but it may begin posteriorly. Five percent develop a small pleural effusion. The importance of this pain is its severity, persistence, and lack of response to salicylates, antibiotics and narcotics. The question has arisen whether it represents rheumatic activation but no proof is at hand. Occasionally, pericardial effusion may develop and aspiration prove necessary.

Auricular fibrillation may develop postoperatively in patients with sinus rhythm prior to surgery[56]. In some, this is only transient. It is for this reason that no attempts should be made to revert fibrillation to regular rhythm prior to operation. In unusual instances, reversion may be spontaneous postoperatively[56]. Attempts to convert to sinus rhythm may be made 1 or 2 months after operation[45].

Experience with the effects of surgery on auscultatory findings varies. The apical diastolic murmur may remain the same, may decrease in intensity or may disappear. It may be inaudible during the first 7 to 10 days. Some consider this decrease as the best clinical index to expected postoperative improvement[80]. But improvement, subjective and objective, has been seen without much change in character of the mitral diastolic murmur. Less often, an increase in intensity of the diastolic rumble is noted, ascribed to an increased rate of blood flow[56]. A mitral systolic murmur, usually grade 1 or 2, often is heard for the first time postoperatively. It is tolerated well, and it is a moot point whether it represents a mitral regurgitation[80]. Where murmurs of mitral insufficiency existed previously, they may remain the same, or on some occasions, decrease. If grade-3 or greater apical systolic murmurs are heard, a poor symptomatic result can be anticipated[80]. The apical diastolic thrill frequently disappears. The intensity of the first heart sound is little affected, despite what happens to the associated murmurs[56,80]. The accentuated pulmonary second sound is little changed too, but the Graham-Steell murmur usually disappears[80]. The latter appears to be a more sensitive index of decreased pressure in the pulmonary circuit than the altered P2. A new systolic murmur (grade 1 or 2) may appear in the pulmonic area, its explanation unknown[80].

Postoperative physiologic studies[30,56] show improvement but rarely complete return to normal. Pulmonary arterial and "capillary" pressures fall toward normal, and total pulmonary resistance may fall too. Subjective improvement is often greater than the alteration in the measurable dynamics

of the circulation. Some patients whose valves could not be dilated or incised at operation also were improved, a fact to be remembered in evaluating results.

The overall mortality figures now are close to 10% in well over 1,000 cases. In the cases with progressive incapacity it is 5 to 10%, (Harken, 3%); in the statically handicapped, even less. In all reported series, improvement in mortality statistics is noted with better selection of patients, improvement of technique, and greater detail in preparation and management of patients before, during and after operation. Patients with pulmonary symptoms without chronic failure have almost uniformly improved[35,38]. In those who improve dyspnea and cough lessen, and orthopnea disappears. Attacks of pulmonary edema decrease or disappear, and hemoptyses do not recur. Some refractory to medical measures become more responsive and amenable to control. The breakdown of the Bailey group of 214 patients through May, 1951[68], showed excellent results in 42%: namely, return to normal existence without drugs except where questionable need for digitalis existed; 33% improved: that is, greater activity associated with fewer symptoms and improved response to treatment; 13% unimproved and 12% dead. Surgical deaths most commonly are due to production of marked mitral insufficiency, hemorrhage, and cerebral emboli. Cardiac standstill, other arrhythmias, adrenal exhaustion and electrolyte imbalance have also been responsible. A study of 100 cases observed for periods of 6 to 36 months[56], using only slightly different criteria from those above, classed results as excellent in 32%, improved in 46%, 9% unimproved, with a mortality of 11%, but only 6.7% in the last 74 cases. Extension of this series to 274 cases as of May, 1952, brought the operative mortality down to 5.8% with marked and sustained improvement in 76% of patients. It is to be hoped that uniform standards of grading patients on a functional basis, such as those of the New York Heart Association, could become uniform practice, so that pooling of statistics from all surgical centers could be possible. This is most essential for a long-term study of the results of valvular surgery and its effect upon the apparently altered life cycle of rheumatic heart disease.

Surgery of Other Valves Affected by Acquired Disease. A recent report by Bailey, Ramirez, and Larzelere[7] has aroused interest in the feasibility of a surgical approach to the treatment of aortic stenosis. The pattern of development with its process of commissural fusion lends itself to dilating procedures without necessary establishment of aortic insufficiency which is poorly tolerated. It does not appear essential to restore the valve aperture to more than 50% of its normal size, to relieve all symptoms. The mortality in 11 patients in whom the valves were dilated by an umbrella type instrument was 36%. There has been no mortality, operative or late, in 9 patients more adequately operated upon, using a new type parallel bar dilator. Six patients had simultaneous commissurotomy for coexisting mitral stenosis, this procedure being done first during a combination attack. Improvement was reported, but no detailed case reports were provided. Since the original report, these authors operated upon 8 additional patients, 4 with concomitant mitral stenosis, with 7 good results and 1 operative death. Angina, syncope, and left ventricular failure would appear to be the indications for surgery.

Surgical treatment of insufficiency of the various valves is still in the experimental stage, and will probably continue there for some time[13]. Grafts

of viable tissue, such as pericardium or vein segments, or use of artificial mechanical valves may prove feasible, if they can be sutured carefully in a dry field under direct vision. This demands the further development of measures that will maintain the circulation extracorporeally.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF FEBRUARY 17, 1953

The Renal and Cellular Response to Acute Experimental Respiratory Alkalosis and Acidosis. J. R. ELKINTON, M.D., R. B. SINGER, M.D., J. K. CLARK, M.D., and E. S. BARKER, M.D. (Chem. Sec. and Renal Sec. of Dept. of Med., Hosp. U. Pa., and Dept. Res. Med. and Dept. Physiol. Chem., Univ. of Pa.). Voluntary *hyperventilation* of ½ or 1 hour by 6 normal subjects caused abrupt changes typical of respiratory alkalosis in arterial blood, including average rise in pH of +0.25, fall in plasma bicarbonate concentration, and fall in calculated pCO_2 to less than 20 mm. Hg. Average urinary responses in 8 to 10 collection periods per subject were: (1) Variable urine flow, the most consistent change being a 60% drop during the first period after hyperventilation. This decrease was abolished in one subject by maintaining an osmotic diuresis (mannitol). (2) A characteristic acid-base response with rise in pH to 7.30 and bicarbonate excretion rate of 192 uEq./min., and fall in ammonia output. (3) Rise in potassium excretion rate of +170 uEq./min., sustained during hyperventilation and steady fall afterward reaching in the final period 50 uEq./min. below the control. (4) Rise in sodium excretion rate of +170, and in chloride +110 uEq./min. in ½ hour of hyperventilation, with subsequent abrupt fall below the control levels, regardless of whether the hyperventilation was continued or not.

In six normal subjects, whole blood pH and plasma CO_2 content were determined, and CO_2 pressure and buffer base concentration were calculated, before, during and after *inhalation of 7.5% CO_2* for approximately 30 minutes. The average change in pH was −0.09, in plasma CO_2 +1.7 mM. per L., in whole blood buffer base −1 mEq./L, and pCO_2 +12 mm. Hg; these changes are characteristic of primary respiratory acidosis. In the 5 subjects whose control urines had been rendered approximately neutral by prior loading with $NaHCO_2$ the urinary pH fell and the titratable acidity rose. At the end of the CO_2 inhalation, the average changes in electrolyte excretion rates over the individual mean control values in uEq. per min., were as follows: HCO_3 = −63, PO_4 = +10, K^+ −71, NH_4^+ +8, (Na^+ −Cl^-) +5. Absolute Na and Cl excretion rates were less consistent but tended to rise. Those changes more or less persisted throughout the 60 to 90 minute periods of observation following the end of the CO_2 inhalation.

The findings are opposite in direction to those observed during acute respiratory alkalosis, and together with those experiments indicate that in respiratory acid-base disturbances, the urinary excretion of bicarbonate correlates positively with blood pH and not with plasma bicarbonate concentration and amount of bicarbonate filtered. They also indicate that potassium predominates in the renal cation response, having a reciprocal relation to hydrogen ion. The cellular cation response in both sets of experiments was assessed as follows. In respiratory alkalosis, the calculated total "effective" extracellular

bicarbonate is decreased and this decrease is associated with a release of hydrogen ion from buffer protein and transfer of hydrogen ion out of, or bicarbonate ion into, intracellular fluid. This latter transfer is approximately equivalent to the calculated movement of sodium out of the "chloride space" into "cells." In respiratory acidosis the opposite set of transfers were found, namely: increased "effective" extracellular bicarbonate, hydrogen ion taken up by buffer protein, hydrogen ion transfered into, or bicarbonate ion out of, intracellular fluid in amounts roughly equivalent to the transfer of sodium out of "cells". Thus acute respiratory acid-base disturbances result in both renal and cellular cation responses, the former involving mainly potassium and hydrogen, the latter sodium and hydrogen or bicarbonate. In relative magnitude, however, the cellular sodium-hydrogen exchange is by far the greatest constituting approximately 90 per cent of the total cation exchange involved.

Studies on the Enzymatic Conversion of Hypoxanthine to Inosinic Acid. E. D. KORN, A.B., and J. M. BUCHANAN, PH.D. (Dept. of Physiol. Chem., Sch. of Med., Univ. of Penna.). Williams and Buchanan (Fed. Proc. Vol. 11, No. 1, 1952) have found that a pigeon liver extract catalyzes the synthesis of inosinic acid from radioactive hypoxanthine, ribose-5-phosphate and adenosine triphosphate. They were able to separate the extract into two fractions (I and II) both of which are necessary for the reaction. Fraction II was replaceable by a crude preparation of rat liver nucleoside phosphorylase. It has now been found that Fraction II may also be replaced by an extract of beef liver acetone powder. Nucleoside phosphorylase has been purified 150-200 fold from this source and the highly purified enzyme cannot replace Fraction II. It has also been found that the enzyme which is active in inosinic acid synthesis can be separated from nucleoside phosphorylase by heating the acetone powder extract at 60° for 5 minutes. Using the most purified system available, 3.5 times as much inosinic acid is synthesized from hypoxanthine as from inosine. These experiments confirm the previous concept that inosine is not on the pathway of inosinic acid formation from hypoxanthine and demonstrate that nucleoside phosphorylase does not function in that reaction. Further studies, which demonstrate that inosinic acid synthesis from inosine is also dependent upon the presence of ribose-5-phosphate, indicate that inosine is not directly phosphotylated by adenosine triphosphate in this system.

Fatty Acid Synthesis in Hyperthyroidism. M. A. SPIRTES, M.D., GRACE MEDES, PH.D., and SIDNEY WEINHOUSE, PH.D. (Institute for Cancer Research and the Lankenau Hospital Research Institute, Philadelphia). Utilizing liver slices from normal and hyperthyroid rats, a study was made of the incorporation of C^{14}-methyl-labeled acetate into the fatty acids of liver slices, in order to test the possibility, suggested by recent experiments of Lardy and Martius, that synthetic reactions might be impaired in hyperthyroidism. White rats weighing 150 to 200 grams were made hyperthyroid either by feeding of dried thyroid or injection of DL-thyroxin. The livers were sliced, placed in Warburg flasks in the presence of 0.01 Molar C^{14}-labeled acetate and the oxygen consumption recorded at 38°C. during a 4-hour experimental period. Conversion of C^{14}-acetate to acetoacetate, CO_2 and fatty acids was measured. Each experiment with hyperthyroid rats was accompanied by one with normal control animals. It was found that oxygen consumption and acetate oxidation were 30 to 60% higher in the hyperthyroid rats. No definite differences in the conversion of acetate

to acetoacetate were observed between normal and hyperthyroid animals. In 20 experiments with hyperthyroid rats, the average incorporation of acetate into liver slice fatty acids was as high as that displayed by normal, concomitant control rats. In view of the fact that conditions associated with low liver glycogens are also associated with low fatty acid synthesis, it was surprising that the "hyperthyroid" livers displayed no impairment in fatty acid synthesis despite the fact that their glycogen levels were considerably below those of the normal rats. In fact, in 5 of 12 fed thyroxinized rats, hepatic lipogenesis was as high on the average as the values found for concomitant, normal animals, despite the fact that their liver glycogen levels were in the range of those displayed by fasting animals. It is concluded that the synthesis of liver fatty acids from acetate is not impaired and may be increased in hyperthyroid rats.

Infrared Spectra of the Liver in Adult and Fetal Rats. H. P. SCHWARZ, M.D., H. E. RIGGS, M.D., C. F. GLICK, PH.D., J. MCGRATH, V.D., R. CHILDS, B.S., E. BEW, JR., B.A., F. STONE, M.S. (Labs. Philadelphia General Hospital). Infrared spectra recorded from frozen and dried sections of the liver of adult and fetal rats showed 2 different types of absorption bands, 1. At high frequency, bands similar to those found in other tissues and in proteins (3.04 u, 3.4 u, 6.0 u, 6.44 u, 6.84 u, 7.20 u and 8.10 u), 2. At low frequency, absorption bands characteristic of liver tissue, namely, 2 weak bands at 8.67 and 10.70 u and 2 strong bands at 9.23 u and 9.54 u (adult liver) and at 9.23 and 9.71 u (fetal liver). Fasting of adult animals caused absence of the 9.54 u band and reduction of a strength of the 9.23 u band; refeeding of those animals with glucose produced a band at 9.56 u; refeeding with sucrose a band at significantly higher wavelength, e.g., 9.70 u. The infrared spectrum of the adult liver thus appears to be very similar to that of the glucose fed animals, and the infrared spectrum of the fetal liver very similar to that of sucrose fed animals. Commercial glycogen showed all the characteristic bands of the liver of adult animals after sucrose feeding and of the fetal liver. The second strong band of the liver spectrum which remained, though greatly reduced, in the fasting animal is not caused by glycogen alone, but also by vibrations of nucleic acids found at the same wavelength, 9.23 u. Quantitative measurements of ratios of densities of the characteristic bands of the liver (9.51 or 9.71 u) to an internal standard band (6.44 u) indicated that the fetal liver at about 2½ week gestation contained considerably higher amounts of glycogen than the liver of adult rats. Roentgen-ray irradiation of the pregnant animals 1 day prior to the experiment and of the adult animals 2 days prior to the experiment did not significantly affect the strength of bands assigned to glycogen. This study was carried out under Contract AT (30-1) 1175 with the U. S. Atomic Energy Commission.

BOOK REVIEWS AND NOTICES

TRANSACTIONS OF THE 11TH CONFERENCE ON THE CHEMOTHERAPY OF TUBERCULOSIS. Pp. 401. St. Louis and Washington: Veterans Administration Area Office and Central Office, 1952.

THIS paper-bound volume is the edited transcript of the latest Conference on the Chemotherapy of Tuberculosis, held in January, 1952, under the joint sponsorship of the Veterans Administration, the Army and the Navy. The meetings, which began in 1946, as a relatively small intramural get-together, are now attended by some 250 physicians and medical scientists from every part of the country. Despite the increase in attendance, the Conference has not modified its original purpose, which is to advance knowledge of chemotherapy and related fields by collective effort. The emphasis has been on cooperative studies conducted voluntarily, but with strict adherence to pre-determined protocols. Randomization of patients has been attempted to permit collation of data obtained on patients treated with various drugs and dosage regimens in many different places.

This report is a compilation of data from 6,000 individual case reports submitted by 44 hospitals; it provides the most up-to-date thinking on the chemotherapy of tuberculosis.

Included in the report are 57 pages of tables and the transcript of 6 miles of tape recording, so it may be appropriate to direct the reader's attention first to the summarizing account in the front of the book and then to the more complete summaries that close the report of each half-day session. A special reward for book reviewers and others who read straight through the text is the indomitable sense of humor of the editor. D. O.

THE PATHOGENESIS AND TREATMENT OF THROMBOSIS. BY IRVING S. WRIGHT, M.D., Professor of Clinical Medicine, Cornell University Medical College, New York. Pp. 78; 4 ills. New York: Grune and Stratton, 1952. Price, $3.00.

THIS concise monograph is both informative and readable. It contains in clear form an excellent summary of present day knowledge of the chemical, physical and morphologic factors in blood clotting.

The role of such factors as malignancy, cryoglobulins, cold hemagglutinins, etc., in thrombosis is outlined.

Anticoagulant therapy with heparin, dicumarol and tromexan is treated in some detail. Newer experimental anticoagulant agents are discussed from the standpoints of rapidity and duration of action, dosage and toxicity. The author who has wide experience in the field, adds his personal appraisal of the medical future of these agents.

A manual for the clinical use of the standard anticoagulants and for the performance of the clinical and laboratory tests necessary for their control is appended. W. S.

A STEREOSCOPIC ATLAS OF HUMAN ANATOMY SECTION I. THE CENTRAL NERVOUS SYSTEM. BY DAVID I. BASSETT, M.D., Associate Professor of Anatomy, Stanford University, California. Color photographs by Wm. B. Gruber. 238 stereoscopic kodachrome photographs with an explanatory line diagram for each one. Portland, Oregon: Sawyer's Inc., 1952. Price, $27.50 includes the four volumes and 34 Reels (238 scenes). Viewmaster stereoscope is an additional $2.00; Sight attachment for Stereoscope, $2.00; Transformer for Light Attachment, $3.00.

IN a series of 34 VIEWMASTER kodachrome reels, Dr. Bassett very adequately illustrates the detailed gross anatomy of the brain and spinal cord. Included are meninges, arteries, and ventricles of the central nervous system. Angiograms and pneumoencephalograms supplement the gross dissections. Each stereoscopic view is explained in the atlas by a line diagram, drawn to scale, and accurately labeled.

The gross specimens, used as a basis for the kodachromes, include numerous dissections of the brain. The material has been especially well chosen, excellently prepared, and beautifully photographed. The atlas is a definite aid to the teaching of anatomy of the central nervous system to medical students, and will be of great value to anyone interested in the field of neurology. Neurosurgeons, clinical neurologists, and radiologists will find the atlas indispensable. D. K.

DISEASES OF THE CHEST. BY T. ROYLE DAWBER, M.D., Senior Surgeon, USPHS, Chief of Heart Disease Epidemiology Study, National Heart Institute, and LLOYD E. HAWES, M.D., Consultant, USPHS Hospital,

Boston. Pp. 440; 216 ills. Baltimore: Williams & Wilkins Co., 1952. Price, $10.00.

In their preface the authors give as their reason for writing this book the need for a text on chest diseases written from a balanced clinical and roentgenological point of view. The authors attempt to fulfill this need by dividing the book about equally between text and reproductions of roentgenograms and by devoting the text to both clinical and roentgenographic features of each disease.

In this reviewer's opinion, the book is mainly successful, insofar as any book written largely about Roentgen rays can hope to succeed; but a major criticism is that the authors attempt to cover too much ground. Almost every condition affecting the thoracic contents is discussed; and for most, a review of etiology, pathology, diagnosis, prognosis and treatment is attempted. This encyclopedic approach imparts a generalizing tone to the text, which is otherwise commendable for being forthright, up-to-date and, with few exceptions, accurate.

The authors have a sound and practical point of view on many disputable questions in the field they cover. Medical students, in particular, should find the book useful as an integrated introduction to the clinical and roentgenological phases of pulmonary disease.

The illustrations are well chosen, and almost uniformly excellent. D. O.

Cybernetics. Transactions of the 8th Conference, March 15-16, 1951. Edited by Heinz von Foerster. Margaret Mead and Hans Lukas Teuber, Assistant Editors. Pp. 240; 11 ills. New York: Josiah Macy, Jr. Foundation, 1952. Price, $4.00.

This volume, the third in a series dealing with circular causal and feedback mechanisms in biological and social systems, records the presentations of seven representatives of major branches of science on the means, methods and problems of communication. In addition, and what is most valuable and instructive, there are recorded the informal discussions of these matters by a larger panel of leading scientists who took part in the 8th Conference under the Macy Foundation. The book should be of interest to all scientists. R. K.

Physical Medicine and Rehabilitation for the Clinician. Edited by Frank H. Krusen, M.D., Professor of Physical Medicine, Mayo Foundation. Pp. 371; 96 ills. Philadelphia: W. B. Saunders Co., 1951. Price, $6.50.

Physical medicine is a rapidly growing branch of medicine. Its value was well illustrated by the results of rehabilitation centers set up by the Armed Forces during World War II. This text by Dr. Krusen and 24 contributors is most timely. It deals with therapeutic application of physical agents, diagnostic applications of physical agents, clinical aspects of clinical medicine, and fundamentals of anatomy and physiology as related to physical medicine. Illustrations are excellent, but in the opinion of the reviewer insufficient in number. The book is of definite value for the general practitioner, physiatrist, and certainly physiotherapists should welcome its publication. A. S.

Disease of the Nervous System in Infancy, Childhood and Adolescence. By Frank R. Ford, M.D., Associate Professor of Neurology, Johns Hopkins University. 3rd ed. Pp. 1216; 255 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $18.50.

This third edition, completely revised and enlarged, is very well illustrated; 20% more illustrations having been added. It is a very complete consideration of the subject although the discussion of some entities is appropriately brief. A most adequate bibliography appears at the end of the description of each disease for those who desire further discussion. Another noteworthy part of the text and reference book is the insertion of case histories throughout. It is heartily recommended for all pediatricians, neurologists and those orthopedists who do pediatric orthopedics. S. G.

Leonardo Da Vinci on Movement of the Heart and Blood. By K. D. Keele, M.D., F.R.C.P., With a Foreward by Charles Singer, M.D., F.R.C.P. Pp. 142; 68 ills. Philadelphia: Lippincott, n.d. Price, $15.00.

The many brilliant sides of Leonardo's character and achievements, artist, engineer, archeologist, geologist, physicist, biologist, lend support to the assertion often made that he had one of the best minds in the whole history of mankind. Dr. Keele, therefore, has made a wise choice in limiting the present study to Leonardo's work in a subdivision of animal anatomy and physiology, especially as broader aspects of his scientific work have already been well presented. As Charles Singer points out in a brief but pregnant Foreword, it is "thus only that the truly modern character of Leonardo's scientific outlook can be adequately appreciated".

For Leonardo to a truly remarkable degree sought anatomical truths untrammeled by falsities and guess work and recorded them with an accuracy that was not again attained for decades and an artistry that has never been surpassed. A collection of notes and sketches, that Leonardo himself recognized as without order but hoped later to arrange, invited the orderly integration which the author here presents.

Chapters on Leonardo's life and art and his attitude toward the physical sciences and the living world lead through a short survey of his approach to anatomy and physiology in general and of ancient authorities on the heart to his own detailed studies.

As Dr. Keele observes, Leonardo never departed from the Galenic concept of the movement of the blood as an ebb and flow, a microcosmic counterpart of the macrocosmic tides; and though disturbed by the amount of blood going through the heart, he disposed of it, the obstacle, with a theory rather than, like Harvey, making it a starting point for investigation. He recognized the importance of the auricles (therefore speaking of 4 ventricles, 2 with "dilatable purses"), also the muscular nature of the heart wall, and many correct details of its systole and diastole in relation to the action of the valves. He was convinced of the impossibility of air entering the heart from the lung. Yet he followed tradition in describing "imperceptible" pores in the inter-ventricular septum and in viewing heat production as the reason for the action of the heart and the parallel ebb and flow of the blood in the arteries and veins. These views palliate such rare errors as joining the right pulmonary vein to the right auricle; then too he may have happened on an anomaly of this kind. His descriptions and delineations of the coronary vessels, the sinuses of Valsalva (long before Valsalva) and of the moderator bands of the right ventricle are excellent, as are those of many other blood vessels throughout the body.

His frequent failures in this field as in aviation and art, his "tragic pursuit of perfection", can justly be attributed in large measure to the difficulties attending dissection and the lack of scientific knowledge at that time, so inadequate to support his demands upon it. His admirers, too, may take solace in the knowledge that even today only a small part of his writings and notes have become available. If they had not had to await the passage of literally centuries for their publication, a mystery which like his mirror writing has never been satisfactorily explained, he might long since have been established as a great pioneer in human anatomy and cardiology.

Dr. Keele's study has been well presented in a pleasant format with good large type on non glare paper, and with numerous excellent reproductions. Especially to be commended is the emphasis brought out on Leonardo's methods of reasoning, whether they arrived at correct or false conclusions. The book is an important addition to knowledge of Leonardo's anatomical studies. It is warmly recommended not only to medical and art historians but also to anatomists, physiologists and clinicians who cherish the long perspective of tradition. E. K.

PRINCIPLES OF ORGANIC EVOLUTION. By ARTHUR WARD LINDSEY, Professor of Biological Sciences, Denison University. Pp. 375; 216 ills. St. Louis: C. V. Mosby Co., 1952. Price, $5.75.

BEGINNING with a resume of the teachings of the early Greek philosophers and continuing through a discussion of modern genetics, Dr. Lindsey weaves the story of modern organic evolution in a clear and vivid manner. He considers, in logical sequence, the relationship of organisms, evidences of evolution, the evolution of plants and animals, foundations of evolution, discussions of the Lamarckian and Darwinian theories, and, finally, the evolution of man.

Principles of Organic Evolution is a scholarly work. It is written so that a broad subject is readily understood and written in a manner that is a pleasure to read. Dr. Lindsey's many years experience, both as a student and a teacher of the biological sciences, is revealed in the way he descriptively illustrates the relationship between organisms and by his ability to interrelate the biological sciences.

The book is quite well illustrated and very well printed, except for the reversing of one figure illustrating the developing veins (4th stage shown in Figure 41, p. 77). As shown, the azygous vein would empty into the coronary sinus. However, this is a minor detail and need not influence the brilliant future the text so much deserves. D. K.

A PSYCHOANALYTIC LAWYER LOOKS AT MARRIAGE AND DIVORCE. By JOHN H. MARIANO. Pp. 276. New York: Council on Marriage Relations, 1952. Price, $3.00.

No one will quarrel with the theme of this book that separation and divorce are not the solution to the breakup of marriages. Rather, says the author, lawyers and the courts should

investigate more deeply the reasons for unhappiness and incompatibility in marriage and try to remedy them whenever and wherever they can.

Unfortunately, this excellent theme is not handled too well in this rather loosely organized book. Choice of terms is often unsatisfactory. What for instance is a "psychoanalytic lawyer?" Is he a lawyer who has been psychoanalyzed or a lawyer who has read psychoanalytic literature and who applies psychoanalytic knowledge to his work? Mr. Mariano speaks of the need for the application of psychoanalytic jurisprudence. What he seems to want to urge is that more professional men meet the problems of marriage and divorce with a greater knowledge of human personality. Admittedly a great deal of knowledge has come from psychoanalysis but a more subtle presentation of the author's interest in and gratitude to psychoanalytic theory might have been better for his cause. O. E.

EXPERIMENTELLE HISTOPATHOLOGIE, EIN EINFUHRUNGSKURS. BY H. MEESSEN, Pathologisches Institut der Medizinischen Akademie Dusseldorf. Pp. 153; 125 ills. Stuttgart: Georg Thieme Verlag, 1952 (Grune & Stratton, Inc., New York, Agents for the United States). Price, DM 22.50.

THIS introduction into experimental histopathology consists of illustrations and descriptions of the lesions of over 100 experimental conditions such as vitamin deficiencies, irradiation damage, toxic states, allergic reactions, wound repair, transplantations, endocrine disorders and experimental oncology. The illustrations are fair. The descriptions are brief, but contain useful information. The references, however, are inadequate. This booklet should be helpful to those who teach experimental pathology. W. E.

HUMAN LOCOMOTION AND BODY FORM. BY DUDLEY J. MORTON, M.D., Formerly Associate Professor, Department of Anatomy, College of Physicians and Surgeons, Columbia University, and DUDLEY FULLER, Associate Professor, Department of Mechanical Engineering, Columbia University. Pp. 285; 82 ills. Baltimore: Williams & Wilkins, 1952. Price, $5.00.

DR. MORTON'S text studies human locomotion and body form in great detail. Historical data as well as anthropological aspects are included. In addition, physiology, physics, and the clinical aspects of motion are dwelt upon. The author is to be commended for his comprehensive study. The illustrations, although adequate, are not too plentiful. This text is more likely to be appreciated by anatomists and those interested in the basic sciences than by the practitioner or student. A. S.

CARBOHYDRATE METABOLISM. A SYMPOSIUM ON THE CLINICAL AND BIOCHEMICAL ASPECTS OF CARBOHYDRATE UTILIZATION IN HEALTH AND DISEASE. Edited by VICTOR A. NAJJAR, Johns Hopkins University Medical School. Pp. 134; 31 ills. Baltimore: The Johns Hopkins Press, 1952. Price, $4.00.

THE contributions of the biochemists and clinical investigators presented in this symposium make available to the reader a great deal of recent knowledge of carbohydrate metabolism. The presentations of Drs. Cori, Sutherland, Hastings and Park, who were among the biochemists represented, deal largely with the enzymatic reactions in carbohydrate metabolism and the effect of hormones and other conditioning factors upon these reactions. The effect of carbohydrate utilization in the rat diaphragm upon potassium uptake; and, the converse, the effect of potassium on carbohydrate metabolism, is presented in a study by Calkins and Taylor. The clinical investigation encompassed in the symposium deals with von Gierke's Disease. Hypoglycemia and Diabetic Acidosis by such authorities as Dorothy Anderson, McQuarrie and Butler. An excellent summary by the editor concludes the volume which should be read by every student of clinical medicine. C. S.

BASIC PRINCIPLES OF CANCER PRACTICE. BY ANDERSON NETTLESHIP, M.D., Professor of Pathology, University of Arkansas. Pp. 398; 106 ills. Baltimore: Williams & Wilkins Co., 1952. Price, $7.00.

AN effort is made to acquaint the general practitioner with the entire field of cancer. Of necessity, 10 of the 19 chapters deal briefly and in generalities of neoplasms affecting body organs or systems. In addition to chapters on cancer diagnosis, clinical pathology, local and systemic effects of cancer, treatment of cancer and cancer in children, three chapters are devoted to "The Status of Present Day Cancer Practice," "How Cancer Research Affects Clinical Cancer Practice," and "Relation of Occupation or Trauma to Cancer."

The latter three chapters deserve attention. A study of the natural history of cancer suggests that a precancerous situation may

exist for a prolonged period. Simultaneously with the growth towards true cancer there is alteration in the biochemical background of the cells and some factor or factors are formed which are capable of producing irreversible multiplication. The agents which are known to be carcinogenic may completely disappear from the new growth.

In cancer research one of our most powerful tools is the various strains of experimental animals which bear cancer. It is assumed that the laws of growth that govern neoplasia in lower species are similar to those in man.

Since 80% or more of the patients are first seen by the general practitioner, early diagnosis and early institution of treatment will remain his responsibility. The author endeavors to demonstrate to the general practitioner how clinical and laboratory procedures should be applied in the establishment of a diagnosis and in the consideration of the treatment modality.

Some of the author's comments and ideas may be disagreed with, nevertheless this book is recommended for its broad approach to the cancer problem. J. B.

STERILITY: ITS CAUSE AND TREATMENT. By J. JAY ROMMER, M.D., Gynecologic Staff, Beth Israel Hospital, Newark, N. J. Pp. 427; 259 ills. Springfield, Illinois: Charles C Thomas, 1952. Price, $12.50.

THE author's purpose in writing "Sterility: Its Cause and Treatment" was to provide a reference book which physicians could use to help solve specific problems in infertility and which covered all aspects of the condition. The range of material is wide and includes both female and male factors; it presents not only a detailed discussion of common causes as tubal obstruction but of minutia such as agglutination of the labiae. The steps in the investigation of an infertile couple are completely detailed and well illustrated. The procedures in such special tests as examinations for tubal potency and endometrial biopsy are carefully explained and their pitfalls indicated.

There are voluminous lists of references, the majority of which antecede 1940 and which fail to bring the subject even close to current investigations. For instance of the 78 references in Chapter X (Means of Investigation in the Infertile Female) all but 11 were prior to 1946 and the latest is 1947. In Chapter XIV (The Medical Treatment of Infertility) of 96 references the latest is 1948 and only 15 were published after 1945. An unqualified statement (page 128) "It is estimated that 20 to 30 per cent of pregnant women subjected to surgery will abort" is derived from Kelly's Medical Gynecology published in 1908.

The author's ventures into general gynecology are sprinkled with misinformation; for example he states that "multiple corpus luteum cysts may be malignant, that both pseudomucinous and serous cysts are unilocular and that an arrhenoblastoma produces large amounts of estrogen".

In general the book suffers from an attempt to be all inclusive. Sketchy summaries of preparation of tissues for microscopic examination and of multiple operative procedures such as those for vesicovaginal fistulae, vaginal tumors, etc. are unnecessary and valueless.

The book is not suitable for students or general practitioners because it fails to differentiate the important from the unimportant. It may be of value to the specialist since it does collect in one volume a great mass of material regarding infertility. Its bibliography is almost valueless as far as recent literature is concerned and little which is new is presented. J. W.

BIOLOGIE, PATHOLOGIE UND THERAPIE DER GELENKE DARGESTELLT AM KNIEGELENK. By ARNOLD SONNENSCHEIN. Assistant, First Surgical Orthopedic University Clinic of Vienna. Pp. 496; 219 ills. Basel: Benno Schwabe & Co., 1952. Price, Fr. 52.

BASED on the rich source material of the Orthopedic University Clinic of Vienna, the author presents the various aspects of the entire gallery of characteristic disease pictures affecting the knee joint. The inclusion of pathologic anatomic illustrations with their corresponding radiograms affords a most instructive exposition of the organic lesions of the joints. A comprehensive review of the course of the abnormal processes in the knee joint serves in addition to elucidate similar processes in other joints. Modern therapeutic methods are likewise evaluated. The text and illustrations leave nothing to be desired. J. H.

NEW BOOKS

Advances in Protein Chemistry. Vol. 7. Edited by M. L. ANSON, Research Division; Lever Brothers Co.; KENNETH BAILEY, Univ. of Cambridge; and JOHN T. EDSALL, Harvard Medical School. Pp. 411. New York: Academic Press Inc., 1952. Price, $8.50.

THIS well-known series continues with a treatment in the present volume of the following topics:

(1) The arrangement of amino acids in proteins by F. Sanger; (2) the structure of collagen fibrils, by Richard S. Bear; (3) muscle contractions and fibrous muscle proteins, by Hans H. Weber and Hildegard Portzehl; (4) the proteins of the mammalian epidermis, by K. M. Rudall; (5) infrared analysis of the structure of amino acids, polypeptides, and proteins, by G. B. B. M. Sutherland; (6) ultra-violet absorption spectra of proteins and amino acids, by G. H. Beaven and E. R. Holiday.

R. H.

Disorders in Perception. By MORRIS B. BENDER, M.D., Prof. Clin. Neurology, New York University College of Medicine. Pp. 109; 5 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $3.00.

THIS monograph, bringing together the previously published papers of the author together with a discussion of work by others, is a must for everyone interested in neurology. The observations on extinction and displacement in sensory perception should be familiar to every worker in the field as well as those in the allied field of psychiatry.

This book is highly recommended. S. G.

Advances in Internal Medicine, Volume 5. By WILLIAM DOCK, M.D., Long Island College of Medicine, and I. SNAPPER, M.D., Mount Sinai Hospital, New York. Pp. 464; 90 ills. Chicago: Year Book Publishers, 1952. Price, $10.50.

"ADVANCES IN INTERNAL MEDICINE" VOL. V maintains the same general level of excellence of the preceding 4 volumes. This annual review fills a real need for those practicing internal medicine, in that it affords an integrated, authoritative review of selected fields in which rapid advancement is occurring. W. S.

A Half Century's Progress Against Tuberculosis in New York City 1900-1950. By GODIAS J. DROLET AND ANTHONY M. LOWELL. Pp. 156; illustrated. New York: New York Tuberculosis and Health Association, 1952. Price, not given.

A comprehensive record presented in text, tables and charts. Interesting information on progress against other diseases and comparisons with other sections of the country are included.

D. O.

Regeneration and Wound-Healing. By A. E. NEEDHAM, M.A., B.Sc., Demonstrator in Zoology, University of Oxford. Pp. 133; 5 ills. London: Methuen & Co. Ltd. New York: John Wiley and Sons, Inc., 1952. Price, $1.75.

THIS book is a very detailed study of regeneration and wound-healing, and takes into consideration wound-healing in all animal life, with a few references to man. The book would appear to be aimed at biologists primarily, and, therefore, is not to be recommended to the practicing physician unless he should have particular interest in this field.

The author's references, his background and grasp of the subject appears to be quite good.

The book might have been made more readable had larger type been used and larger spacing.

R. T.

Body Temperature. By W. A. SELLE, PH.D., University of California Medical School. Pp. 112; 23 ills. Springfield: Charles C Thomas, 1952. Price, $3.50.

THIS important member of the American Lecture Series is up to the usual high standard of this group. The author is a competent, careful observer and the presentation is excellent. The book stresses man's physiological adaptation to his environment. Besides the usual divisions on heat production and loss, control, internal and environmental disturbances, the author has included one on physical allergy. This is a useful contribution. M. O.

Tuberculosis. By SAUL SOLOMON, M.D., Assoc. Clin. Professor of Medicine, New York University Post-Graduate Medical School. Pp. 300; 7 ills. New York: Coward-McCann, Inc., 1952. Price, $3.50.

THIS is the second volume of the "Health Series", non-technical books on medical subjects for the general reader. The author covers all important aspects of Tuberculosis. His approach is sound and sensible, his language clear and simple. No effort is made to minimize the seriousness of the disease in spite of continuous advances in treatment. Collapse and resection treatment are discussed but not extolled as replacing bed rest or drugs. The chapter on Isoniazid quotes some of the spectacular case histories from the earliest reports, but ends with a series of unanswered questions. Both sides of the still controversial subject of B.C.G. are fairly presented, one feels that the author leans toward the views of J. Arthur Myers.

Sections on "The Psychology of the Patient", "Rehabilitation", and a final chapter ambitiously called "A Program to Wipe Out Tuberculosis" are very well conceived.

A Glossary is appended, which extends, appropriately, from "Acid Fast" to "Ziehl-Neelson."

This book should prove valuable to patients with tuberculosis, their families, and to all non-medical people interested in Public Health or in any aspect of the tuberculosis problem. R. C.

Preliminary Report on the World Social Situation with Special Reference to Standards of Living. United Nations, Department of Social Affairs. Pp. 180. New York: Columbia University Press, 1952. Price, $1.75.

MUCH of the information given in this excellent report was provided by governments seeking to improve their social conditions. It does not attempt, however, to present systematic analysis of social legislation and social security systems, welfare and health programs, community development projects, and so forth, although references to these topics are occasionally made along with trends and improvements in conditions. Nor are human rights, crime and delinquency, narcotics addiction and similar problems included. After an introductory chapter and a background chapter on population, the report deals with these factors on a subject-matter basis: health, food and nutrition, housing, education and communication, conditions of work and employment, special problems affecting living standards, and general levels

of income and welfare, with concluding chapters devoted to regional approaches in order to gain a general picture of living conditions in particular areas. Throughout the report, the stress is upon social conditions in the economically less-developed areas, because it is in these areas that the needs are greatest. J. K.

Lipid Metabolism, Biochemical Society, Symposia No. 9. Edited by R. T. WILLIAMS. Pp. 102; 7 ills. New York: Cambridge University Press, 1952. Price, $2.75.

THE current number of these symposia is a valuable addition to the armamentarium of the students of fat metabolism. The participants are outstanding workers in the field. The contents include: mechanisms of fat absorption, comparative aspects of lipid absorption and excretion, defective fat absorption in man, fat synthesis from small molecules, aspects of fat metabolism in the ruminant with special reference to the biosynthesis of milk fat, enzymic oxidation of fatty acids, and essential fatty acids and their relation to pyridoxine. The references supplied will be found very valuable. M. O.

First Report, Joint Expert Committee on the Physically Handicapped Child. World Health Organization Technical Report Series No. 58. Pp. 26. Geneva: World Health Organization, 1952. Price, $.20.

First Report of Expert Committee on Trachoma. World Health Organization Technical Report Series No. 59. Pp. 22. Geneva: World Health Organization, 1952. Price, $.15.

Oh Nurse! BY ED. THUNEN AND DON SKINNER. Cartoons by ED. THUNEN. Pp. 62. San Francisco: Harr Wagner Publishing Co., 1952. Price, $1.00.

Good for some chuckles by doctors and patients. R. K.

Beiträge zur Zellulartherapie. Festschrift zum 70 Geburtstag von Dr. med. Paul Neihans, La Tour de Peilz, Switzerland. Pp. 132. Munich: Urban & Schwarzenberg, 1952. Price, not given.

A Vitamin Digest. BY GUY W. CLARK. Technical Director, Lederle Laboratories Division, American Cyanamid Co. Pp. 254; 2 ills. Springfield, Ill.: Charles C Thomas, 1953. Price $6.50.

THIS text provides a background knowledge of the vitamins and their individual biologic significances. However, the biochemical data presented for each of these nutritional catalysts, in most instances, do not represent the recent advances in this field. Pantothenic acid as a component of the acetylating enzyme system and pyridoxine as a factor involved in amination and transamination reactions are not discussed in these respective chapters. The newer concepts of the actions of the fat soluble vitamins are not reviewed. The clinical descriptions of vitamin deficiency states are inadequate. It is felt that a monograph of this type should contain more of the recent biochemical and metabolic data and should have a well-organized clinical section. C. S.

Neuronenlehre und Zellenlehre. BY PROF. DR. MED. HUGO SPATZ. Pp. 40; 10 ills. Munich: J. F. Lehmanns Verlag, 1952. Price, DM 4.

THIS is one among others of brochures or articles in honor of the hundredth anniversary of the birth of Santiago Ramón y Cajal. Its distinguished author has expressed the subject of the neuron doctrine and the cell doctrine very thoroughly, presenting also the views of Neissl, Apathy, Bethe, Boerke, and other opponents of Ramón y Cajal's neuron doctrine. He is one of the school who ascribes the chief element in regeneration of nerves to the presence of the nucleus in the nerve cell. M. M.

NEW EDITIONS

Synopsis of Pathology. BY W. A. D. ANDERSON, M.D., Prof. of Pathology, Marquette University School of Medicine. 3rd ed. Pp. 788; 334 ills., and 13 color plates. St. Louis: C. V. Mosby Co., 1952. Price, $8.00.

ANDERSON'S "little giant" is one of the few successful synopses in any medical specialty. It has enjoyed this popularity not so much because it is a synopsis but because it is a text that looks and feels like a synopsis. Most medical people, other than pathologists, themselves, are too busy, too lazy or too uninformed to dig through the rapidly increasing complexities of the average pathology text. They long for a short cut and Dr. Anderson has provided one for those who are frightened by his larger volume. Most compends are worthless because they fail to supply a true picture of the whole. This volume by and large avoids this pitfall because it is not really a compend but rather a short text. The text is lucid, the pictures are clear and illustrative and the material is well chosen. If the subject continues to increase in complexity we may be compelled to teach a preliminary course in basic pathology with this sort of book. E. A.

Applied Physiology. BY SAMSON WRIGHT, MONTAGUE MAIZELS, AND JOHN B. JEPSON. University of London, Middlesex Hospital Medical School; University College Hospital Medical School; Courtauld Hospital Medical School. 9th ed. Pp. 1190; 688 ills. New York: Oxford University Press, 1952. Price, $9.00.

THE ninth edition of this valuable book keeps unbroken a series which has been most useful to practitioners, scientists and medical students for many years. This edition has been so extensively rewritten that it may be considered as a new book. The arrangement of subject matter is different than in former editions. The illustrations have always been admirable and this edition contains approximately 200 more of the same high quality. These are often redrawn for teaching clarity and are from recent work. The references are to a few of the most important papers in each field and give the interested person a starting point from which the whole area of interest may be explored. This book can be recommended without reservation. M. O.